Quantitative Electroencephalography and Genetics as Biomarkers of Dementia in Parkinson's disease

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Abstract

The importance of cognitive decline in Parkinson's disease (PD), which eventually progresses to dementia (PD-D) in the majority of surviving patients, has been widely recognised during the last decade. PD-D is associated with a twofold increase in mortality, increased caregiver strain and increased healthcare costs. Thus, early and correct identification of the PD patients with a risk of dementia is a challenging problem of neurology, which has led to the suggestion of various markers of cognitive decline in PD. If validated, these markers would offer the opportunity for disease modification and therapeutic intervention at a critical early stage of the illness, when the viable neuronal population is greater.

The focus of this thesis was to assess how various factors - quantitative electroencephalography (qEEG) changes, genetics, deep brain stimulation (DBS), olfactory function, etc. – may be related with the risk of cognitive decline in PD patients. We performed four clinical studies with various design. These studies included PD patients who were dementia-free on inclusion, and control participants.

Principal findings are the following: (1) increase of global median relative power theta (4–8 Hz), executive and working memory dysfunction are independent prognostic markers of severe cognitive decline in PD patients over a period of 3 years. (2) DBS of the subthalamic nuclei in a group of PD patients with mean age 63.2 years, in comparison with a group of younger patients (52.9 years), causes higher incidence of psychiatric events over 2 years of observation. However, these events were transient and did not outweigh the benefits of surgery. (3) Worsening of verbal fluency performance is an early cognitive outcome of DBS of the subthalamic nuclei in PD patients. (4) Among early appearing non-motor signs of Parkinson's disease, alteration of olfaction but not EEG spectrum correlates with motor function. (5) A composite score approach seems to be a realistic goal in the search for biomarkers of severe cognitive decline.

Keywords: ***Parkinson's disease (PD), dementia, biomarkers, quantitative electroencephalography (qEEG), deep brain stimulation (DBS)***

Page 4 (Aknowledgements) contains private information and therefore is not available in the online version.

Contents

Abbreviations

- AD = Alzheimer's disease
- APOE = apolipoprotein E
- ATP13A2 = probable cation-transporting ATPase 13A2
- ATR = alpha/theta ratio

- AUC = area under the curve
- BDI-II = Beck Depression Inventory, revision II
- BPRS = Brief Psychiatric Rating Scale
- CAF = Clinical Assessment of Fluctuations
- CAMCOG = Cambridge Cognitive Examination
- CC = Clustering Coefficient
- CI-OCS = change index in overall cognitive score
- COMT = Catechol-O-Methyltransferase
- CSF = cerebrospinal fluid
- DBS = deep brain stimulation
- DF = dominant frequency
- DFV = dominant frequency
- DJ-1 = protein deglycase
- DLB = dementia with Lewy bodies
- DNA = deoxyribonucleic acid
- DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4^{th} edition
- EEG = electroencephalography
- EIF4G1 = eukaryotic translation initiation factor 4 gamma 1
- FBX07 = F-box protein 7
- FDG = ^{18}F-deoxyglucose
- GBA = glucosylceramidase Beta
- GFS = global field synchronization
- GIGYF2 = GRB10 Interacting GYF Protein 2
- GPi = globus pallidus internus
- GPi-DBS = deep brain stimulation of the globus pallidus internus
- GRMP = global relative median power
- GRP = global relative power
- GWAS = genome-wide association studies
- HC = healthy controls
- HGNC = HUGO Gene Nomenclature Committee
- HTRA2 = HtrA serine peptidase 2
- LDLRAD1 = low density lipoprotein receptor class a domain containing 1
- LED = levodopa equivalent daily dose
- LRRK2 = leucine-rich repeat kinase 2
- MAPT = microtubule associated protein Tau
- MCI = mild cognitive impairment
- MDA = mean decrease accuracy
- MDGC = mean decrease gini coefficient
- MDS = International Parkinson and Movement Disorders Society
- MEG = magnetoencephalography
- MF = Median Frequency
- miR-4781 = microRNA 4781
- MMSE = Mini-Mental State examination
- MPTP = 1-methyl-4-pheyl-1,2,3,6-tetrahydropyrine
- NMDA = N-methyl-D-aspartate
- NMS = Non-Motor Symptoms scale
- OCI = Obsessive-Compulsive Inventory
- OCS = overall cognitive score
- PD = Parkinson's disease
- PD-D = dementia in Parkinson's disease
- PD-DF = Parkinson's disease with dementia with cognitive fluctuations

- PD-DnF = Parkinson's disease with dementia without cognitive fluctuations
- PD-MCI = mild cognitive impairment in Parkinson's disease
- PDmutDB = Parkinson disease Mutation Database
- PDNC = Parkinson's disease with normal cognition (without cognitive impairment)
- PDQ39-EWB = compartment "Emotional well-being" of the Parkinson's disease Questionnaire with 39 items
- PDwD – Parkinson's disease without dementia (no information on MCI)
- PINK1 = PTEN-induced putative kinase 1
- PL = Path Length
- PLA2G6 = calcium-independent phospholipase A2
- PLA2G6 = phospholipase A2 group VI
- PLI = Phase Lag Index
- PVFC = Phonemic verbal fluency: correct answers
- qEEG = quantitative electroencephalography
- REM = rapid eye movements
- RNA = ribonucleic acid
- SAE = serious adverse events
- SCD = subjective cognitive decline
- SL = Synchronization Likelihood
- SLC41A1 = solute carrier family 41 member 1
- SNCA = alpha–synuclein
- SnSc = Sniffing score
- SNPs = single nucleotide polymorphisms
- SPECT = single-photon emission computed tomography
- SPR = sepiapterin reductase
- STN = subthalamic nuclei
- STN-DBS = deep brain stimulation of the subthalamic nuclei
- SVFC = Semantic verbal fluency test: correct answers
- TAPWMO = Test of Attentional Performance – Working Memory (2-back task): omissions
- TCEANC2 = transcription elongation factor A N-terminal and central domain containing 2
- TMEM59 = transmembrane protein 59
- TMTA = Trail Making Test time for part A
- UCHL1 = ubiquitin carboxy-terminal hydrolase L1
- UPDRS = Unified Parkinson's Disease Rating Scale
- UPDRS-III = subsection III (motor examination) of the Unified Parkinson's Disease Rating Scale
- VF = verbal fluency
- VPS35 = vacuolar protein sorting 35
- VTA = volume of tissue activated
- WCST = Wisconsin Card Sorting Test: correct categories

Chapter 1. Introduction

The burden of dementia in Parkinson's disease

Parkinson's disease (PD) is a degenerative disease of the central nervous system, which has motor and non-motor features (*Capriotti and Terzakis, 2016*). Historically PD was considered a disease, which affects mainly motor functions of the patients; however, nowadays it is aknowledged, that non-motor symptoms of PD also have a dramatical impact on the quality of life and disability of the patients (*Khoo et al., 2013*). The importance of cognitive decline in PD, which eventually progresses to dementia in the majority of surviving patients, has been widely recognised during the last decade (*Aarsland et al., 2017; Aarsland and Kurz, 2010; Kim et al., 2009; Riedel et al., 2008*). Dementia in PD (PD-D) is associated with a twofold increase in mortality (*Levy et al., 2002*), increased caregiver strain (*Aarsland et al., 2007*) and increased healthcare costs (*Vossius et al., 2011*). Thus, early and correct identification of the PD patients with a risk of dementia is a challenging problem of neurology, which has led to the suggestion of various markers of cognitive decline in PD (*Mollenhauer et al., 2014*). Currently, genetics and quantitative electroencephalography (qEEG) are gaining research interest as a source for potential risk markers of PD-D (*Aarsland et al., 2017*). There have been reports that slowing of EEG frequency some and genetic variants are associated with cognitive decline in PD (discussed in Chapter 3).

Deep brain stimulation and cognitive decline in Parkinson's disease

In recent years, it has been largely acknowledged that deep brain stimulation (DBS) — a neurosurgical implantation of an electrical pulse generator with electrodes projected to specific targets in the brain — can alleviate motor symptoms of PD, though the exact mechanisms of therapeutic effects of DBS are still not fully resolved (*Garcia et al., 2013*). Cognitive impairment in PD is a limiting factor for the selection of candidates for DBS, also evidence has been accumulating that DBS itself can result in worsening of cognitive performance (*Massano and Garett, 2012*). Some research groups suggested that such worsening may be owing to a "microlesion" of the brain tissue, produced by the passage of the electrodes during implantation (*Maltete et al., 2008*). Other researchers have suggested that post-DBS cognitive decline may be related to the age of the patient (*DeLong et al., 2014*). Further studies and critical analyses regarding the relation of DBS and cognitive decline in PD are warranted to provide much needed clinical evidence and guide future health care policy.

Aims of the thesis

The general aim of the thesis was to investigate the value of genetic and qEEG markers to identify PD patients with a risk of dementia. Within this main research focus, we also investigated the influence of DBS and advancing age on cognitive decline in PD. The list of studies carried out within this research is provided below.

Study I (systematic review): review of the literature concerning qEEG markers of cognitive decline. A search for peer-reviewed original studies in the period 2000 – 2015 was performed. **We planned to compare the obtained data with the findings from our study II.**

Study II (observational longitudinal (cohort) study): investigation of a three-years cohort of patients with PD with regard to finding clinical and neurophysiological markers of cognitive decline. The hypothesis was that **slowing of EEG** (*identified by mathematical processing and calculation of global frequency power*) **precedes clinical onset of severe cognitive decline in PD patients**.

Study III (observational case-control study): investigation of the early cognitive outcomes of DBS in PD patients. We checked for the decrease in cognitive task performance in patients with PD after six months after DBS to the subthalamic nuclei (STN), and compared these patients to non-operated PD patients. The **hypothesis was that DBS is associated with a decrease of verbal fluency cognitive task performance**.

Study IV (retrospective cohort (and case-control) study): investigation of the late outcomes of DBS in PD patients with regard to the age at operation. I retrospectively checked the two-years' clinical and neuropsychiatric outcomes in a group of PD patients with DBS to the STN (STN-DBS) with regard to the age of the participants. The **hypothesis was that age has no negative effects on the neurological outcomes of DBS**.

Study V (cross-sectional study): investigation of the olfactory function with regard to qEEG features and cognitive function of PD patients. I checked olfactory function and its relation to motor and qEEG parameters in patients with PD and healthy controls. The **hypothesis was that olfactory decline in PD correlates with clinical and qEEG parameters.**

Outlines of the thesis

Following this introduction, the thesis begins with a chapter on background (*Chapter 2*), in which we provide an overview on most important aetiological and pathophysiological features of PD, cognitive decline in the context of PD, and markers of such decline. In Chapter 3 we give a detailed overview on known genetic and qEEG markers of dementia and cognitive decline in PD. The following chapters - from 4 to 9 - contain the core methodological contributions of this thesis. Chapter 4 deals with the results of the systematic review of peer-reviewed literature on qEEG markers of PD related cognitive impairment. Chapter 5 presents the results of my core study – observation of patients with PD by means of genetic and qEEG analyses with PD-D as primary outcome. Chapters 6-8 present the results of the substudies, focused on investigation the relation of DBS, age and olfaction with cognitive fucntions and qEEG changes. Chapter 9 contains integrated discussions and conclusions of this thesis.

List of publications within the thesis

A. Full journal articles

[1][1] **Cozac, V.V.**, Chaturvedi, M., Hatz, F., Meyer, A., Fuhr, P., Gschwandtner, U. (2016). Increase of EEG spectral theta power indicates higher risk of the development of severe cognitive decline in Parkinson's disease after 3 years. *Frontiers in Aging Neuroscience.* 8:284. DOI: 10.3389/fnagi.2016.00284;

[1] With permission of respective publishing offices the following publications are included into this thesis.

[2][1] **Cozac, V.V.**, Gschwandtner, U., Hatz, F., Hardmeier, M., Rüegg, S., Fuhr, P. (2016). Quantitative EEG and Cognitive Decline in Parkinson's Disease. *Parkinson's Disease* 1-14, Article ID 9060649. DOI: 10.1155/2016/9060649;

[3][1] **Cozac, V.V.**, Ehrensperger, M.M., Gschwandtner, U., Hatz, F., Meyer, A., Monsch, A.U., Schuepbach, M., Taub, E., Fuhr, P. (2016). Older Candidates for Subthalamic Deep Brain Stimulation in Parkinson's Disease Have a Higher Incidence of Psychiatric Serious Adverse Events. *Frontiers in Aging Neuroscience*. 8;8:132. DOI: 10.3389/fnagi.2016.00132;

[4][1] **Cozac, V.V.**, Schwarz, N., Bousleiman, H., Chaturvedi, M., Ehrensperger, M.M., Gschwandtner, U., Hatz, F., Meyer, A., Monsch, A.U., Taub, E., Fuhr, P. (2015). The Verbal Fluency Decline After Deep Brain Stimulation in Parkinson's Disease: Is There an Influence of Age? *Movement Disorders Clinical Practice*. 3: 1. 48-52. DOI: 10.1002/mdc3.12231;

[5][1] **Cozac, V.V.**, Auschra, B., Chaturvedi, M., Gschwandtner, U., Meyer, A., Welge-Lüssen, A., Fuhr, P. (2017). Among Early Appearing Non-Motor Signs of Parkinson's Disease, Alteration of Olfaction but Not Electroencephalographic Spectrum Correlates with Motor Function. *Frontiers in Neurology.* DOI: 10.3389/fneur.2017.00545

[6] **Cozac, V.V.**, Rotaru, L. (2016). [Paradoxical kinesia in Parkinson's disease: theories and practical application]. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova*. 116(2):109-15. Russian. DOI: 10.17116/jnevro201611621109-115;

[7] **Cozac, V.V.** (2016). [Modern approaches to treatment of psychosis in Parkinson's disease. Review]. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova*. 116(10): 103-109 Russian. DOI: 10.17116/jnevro2016116101103-109;

B. Abstracts at international meetings

[1] **Cozac, V.V.,** Chaturvedi, M., Hatz, F., Meyer, A., Nowak, K., Gschwandtner, U., Fuhr, P. (2016) Correlation of the EEG frequency with cognitive performance in Parkinson's disease – six-months follow-up. Parkinsonism and Related Disorders. 22;2:e143. DOI: 10.1016/j.parkreldis.2015.10.598, (*presented at the XXIth World Congress on Parkinson's Disease and Related Disorders, Milan, Italy*);

[2] Chaturvedi, M., Bousleiman, H., **Cozac, V.V.,** Gschwandtner, U., Hatz, F., Meyer, A., Schindler, C., Zimmermann, R., Fuhr, P. (2016). Quantitative EEG in patients with Parkinson's Disease (PD) with and without Mild Cognitive Impairment (MCI) – Power analysis. *Clinical Neurophysilogy. 127;3:e30-e31.* DOI: 10.1016/j.clinph.2015.11.092, (*presented at the 15th European Congress on Clinical Neurophysiology, Brno, Czech Republic*);

[3] **Cozac, V.V.,** Bogaarts, J.G., Chaturvedi, M., Gschwandtner, U., Hatz, F., Meyer, A., Fuhr, P. (2016). Influence of age on quantitative EEG in Parkinson's disease. Proceedings of the 11th International congress on non-motor Dysfunctions in Parkinson's disease and related disorders (NMPD-D 2016), Ljubljana, Slovenia;

[4] Sturzenegger, R., Meyer, A., Chaturvedi, M., **Cozac, V.V.**, Hatz, F., Gschwandtner, U., Fuhr, P. (2016). Alertness as assessed by clinical testing and alpha reactivity does not correlate with executive function decline in Parkinson's disease (PD). Parkinsonism and Related Disorders. 22;2:e164-5. DOI: 10.1016/j.parkreldis.2015.10.395, (*presented at the XXIth World Congress on Parkinson's Disease and Related Disorders, Milan, Italy*);

[5] Chaturvedi, M., Hatz, F., Meyer, A., **Cozac, V.V.,** Gschwandtner, U., Roth, V., Fuhr, P. (2016). Can Quantitative EEG (QEEG) differentiate patients with Parkinson's disease (PD) from healthy

controls? Parkinsonism and Related Disorders. 22;2:e143. DOI: 10.1016/j.parkreldis.2015.10.388, (*presented at the XXIth World Congress on Parkinson's Disease and Related Disorders, Milan, Italy*);

[6] **Cozac, V.V.,** Chaturvedi, M., Gschwandtner, U., Hatz, F., Meyer, A.., Nowak, K., Sturzenegger, R., Fuhr, P. (2016). Predictive performance of EEG theta spectral power over developing dementia in Parkinson's disease. (*presented at the 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany*);

[7] Meyer, A., Gschwandtner, U., **Cozac, V.V.,** Hatz, F., Fuhr, P. (2016). How do cognitive profiles differ in patients with Parkinson's disease with cognitive decline in comparison to patients remaining cognitively stable? Preliminary results of a 3 years follow-up study. (*presented at the 20th International Congress of Parkinson's Disease and Movement Disorders, Berlin, Germany*).

[8] **Cozac, V.V.,** Bogaarts, J.G., Chaturvedi, M., Meyer, A., Rytz, M., Hatz, F., Gschwandtner, U., Fuhr, P. (2017). Olfactory deficits and the EEG-frequency bands in Parkinson's disease. DOI: 10.1016/j.clinph.2017.06.201, (*presented at the 61st Congress of German Society of Clinical Neurophysiology, Leipzig, Germany*).

[9] Chaturvedi, M., Hatz, F., Gschwandtner, U., Meyer, A., **Cozac, V.V.,** Bogaarts, J.G., Roth, V., Fuhr, P. (2017). Quantitative EEG and neuropsychological tests to differentiate between Parkinson's disease patients and healthy controls with Random Forest algorithm. DOI: 10.1016/j.clinph.2017.06.202, (*presented at the 61st Congress of German Society of Clinical Neurophysiology, Leipzig, Germany*).

Chapter 2. Parkinson's disease and dementia: outlines

Clinical features of Parkinson's disease

As discussed in Chapter 1, PD has motor and non-motor symptoms. The cardinal motor symptoms of PD are: rest tremor, muscular rigidity, slowness of movement (bradykinesia), and postural and gait instability (*Jankovic, 2008*). The prevalence of certain type of motor symptoms varies from patient to patient; thus, some researchers attempted to classify PD according to dominant motor symptoms (*Marras and Lang, 2013*). The following motor subtypes were suggested: tremor-dominant (with a relative absence of other motor symptoms), non-tremor-dominant (sometimes described as akinetic-rigid syndrome), and a mixed subtype.

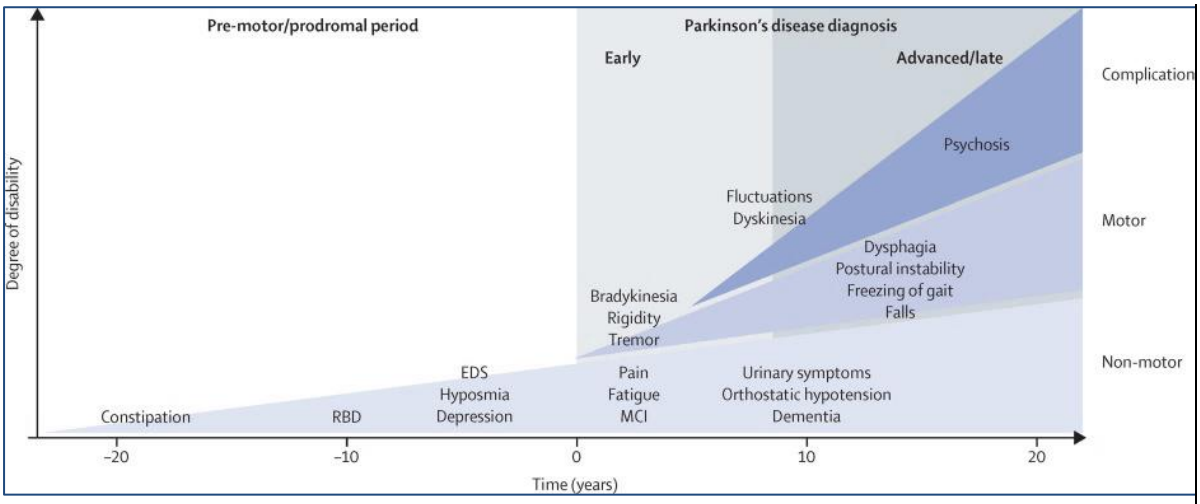
Non-motor symptoms of PD comprise a wide range of disorders: neuropsychiatric symptoms, sensory symptoms, gastrointestinal symptoms, dopaminergic drug-induced behavioural symptoms, sleep disorders, fatigue, autonomic dysfunction, and nonmotor fluctuations (*Chaudhuri et al., 2011*). As in case of motor symptoms, non-motor symptoms of PD are heterogenous, and some researchers attempted to classify PD in accordance with dominant non-motor symptom. Thus, the following non-motor phenotypes of PD were suggested: cortical (cognitive impairment dominant), limbic (comprises subtypes with depression, fatigue, pain, and weight-loss), and brainstem (comprises subtypes with sleep impairment, and autonomic disorders) (*Sauerbier et al., 2016a*).

Non-motor symptoms are frequently present in before the onset of motor symptoms in PD, sometimes for years (*Postuma et al., 2012; Sauerbier et al., 2016b*). Thus, the clinical course of PD is divided in premotor (or prodromal) stage and motor stage (Figure 1; *Kalia and Lang, 2015*).

Epidemiology of Parkinson's disease

The prevalence of PD ranges (per 100'000 inhabitants) from 35.8 to 12'500.0 depending on the region (*Zou et al., 2015; Muangpaisan et al., 2009; von Campenhausen et al., 2005*). PD has a clear age-dependent prevalence (per 100'000 inhabitants): it is 41 in the 40-49 years population group and 1'903 in older than 80 years old (*Pringsheim et al., 2014*). The life risk of PD is 2% for males and 1.3% for females (*Elbaz et al., 2002*), and in the 50-59 years old group the prevalence in males is 3.3 times higher than in females (*Pringsheim et al., 2014*). Median age of disease onset is 60 years (*Lees et al., 2009*), with median time from symptom onset to death of just over 12 years (*Hely et al., 2005, 2008*). The commonest cause of death in patients with PD is pneumonia (*Beyer et al., 2001; Hely et al., 2005*).

Figure 1. Clinical symptoms and time course of Parkinson's disease progression.



Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behaviour disorder.

With permission from Elsevier (source: Kalia and Lang, 2015)

Aetiology of Parkinson's disease

The precise cause of PD, despite decades of intensive study, is still the subject of research (*Przedborski, 2017*). Some proportion of cases of PD is related to genetic factors (*Redenšek et al., 2017*), another proportion – to environmental and lifestyle factors, e.g. exposure to toxicants, depression, head injury (*Goldman, 2014; Lill and Klein, 2017*). In most cases no specific cause is identified and the disease is referred to as *idiopathic PD*[2]. However, it is likely that PD is caused by a combination of genetic and environmental causes (multifactorial origin).

Genetic factors of Parkinson's disease

Genetic factors have been estimated to explain about 5% of the genetic variance of PD, while the common heritable component of PD estimated with missing heritability analysis explained 27% of PD (*Keller et al., 2012*). Even more, some leading researchers consider that genetics is a central component to every case of PD using an illustrative hyperbole "*if you're not working with genetics, you're not working on Parkinson's disease*" (*Singleton et al., 2017*). In the genetic nomenclature of PD, chromosomal regions which contain genes associated with PD – these regions are also called *loci* (sing. *locus*) – were termed "PARK" and numbered in chronological order of their discovery (e.g. PARK1, PARK2 etc.). A large meta-analysis based on genome-wide association studies (GWAS) has identified 24 loci associated with risk for PD (*Nalls et al., 2014*). With the increase of possible genetic associations and combinations due to the research advance, not all of those loci are termed PARK. Mutations in some of these genes cause PD by the nature of the things: they

[2] Greek: idios – one's own + pathos – disease; literally "*a disease of its own kind*".

are called causal genes, and cause monogenic forms of PD. Currently, mutations in five loci are known as confirmed monogenetic factors of PD and are listed in the Parkinson disease Mutation Database (PDmutDB) (Table 1) (*Parkinson Disease Mutation Database (PDmutDB, available online[3]); Cruts et al., 2012*).

In case of some other genes, the association with PD is less conclusive and these genes are the subject to ongoing research (Table 2). Usually such genes are referred to as risk factors or susceptibility loci of PD.

In addition, the concept of *epigenetics* gained attention in recent years in the research of PD. The term „epigenetics"[4] refers to stable and heritable changes in gene expression (phenotype) without any mutation of this gene. Such changes occur through different mechanisms: chemical (covalent) modifications of DNA (e.g. methylation, acetylation), formation of non-coding RNA, and histone modifications (*Ciceri et al., 2017*).

Table 1. Confirmed monogenetic associations of PD
HGNC - Human Genome Organisation Gene Nomenclature Committee; ADom - autosomal-dominant; ARec - autosomal-recessive

Gene	HGNC	No of identified mutations	Type of Mendelian inheritance[5]	Reference[6]
Alpha-synuclein	PARK1/ PARK4[7]	27	ADom	Polymeropoulos et al., 1997
Parkin	PARK2	214	ARec	Hattori et al., 1998
PINK1	PARK6	138	ARec	Groen et al., 2004
DJ-1	PARK7	28	ARec	Abou-Sleiman et al., 2003
LRRK2	PARK8	128	ADom	Zimprich et al., 2004

Table 2. Unequivocal genetic associations or risk factors of PD
HGNC - Human Genome Organisation Gene Nomenclature Committee

Gene	HGNC	Reference
Unidentified, possible SPR	PARK3	Gasser et al., 1998; Sharma et al., 2006
UCHL1	PARK5	Leroy et al., 1998
ATP13A2	PARK9	Schneider et al., 2010
Unidentified, possible TCEANC2, TMEM59, miR-4781, LDLRAD1	PARK10	Hicks et al., 2002; Beecham et al., 2015
GIGYF2 (?)[8]	PARK11	Pankratz et al., 2002
Unidentified	PARK12	Pankratz et al., 2003
HTRA2	PARK13	Strauss et al., 2005

[3] http://www.molgen.vib-ua.be/PDMutDB/default.cfm?MT=1&ML=0&Page=PDmutDB
[4] Greek: epi – outside + genetics; literally "*in addition to genetics*".
[5] It should be stressed, however, that in clinical practice the pedigrees rarely follow a strict Mendelian pattern due to such factors as reduced penetrance, variable expressivity and phenocopy phenomena (*Klein and Westenberger, 2012*)
[6] Only the first publication in chronological order of appereance is shown, for a full list list of related references please access *PDmutDB online database*;
[7] Locus PARK4 was designated as a novel chromosomal region in 1999, but later was found to be identical with PARK1 (*Singleton et al., 2003*).
[8] Initial reports on associations of GIGYF2 with PD were contested (*Di Fonzo et al., 2009b*);

PLA2G6	PARK14	Paisán-Ruiz et al., 2009; Lu et al., 2012; Miki et al., 2017
FBX07	PARK15	Di Fonzo et al., 2009a; Lohmann et al., 2015
Unidentified, possible SLC41A1	PARK16	Wang et al., 2017
VPS35	PARK17	Tsika et al., 2014; Khurana et al., 2017
EIF4G1	PARK18	Chartier-Harlin et al., 2011
GBA	GBA	Sidransky and Lopez, 2012
MAPT	MAPT	Valenca et al., 2016
COMT	COMT	Jiménez-Jiménez et al., 2014
APOE	APOE	Wilhelmus et al., 2011

Environmental factors of Parkinson's disease

A number of environmental factors are associated with the development of PD; they include: exposure to toxins (metals, pesticides, solvents), rural living and agricultural occupation (which are presumed indirect measures of exposure to toxins), head injury, stress and depression (*Kwakye et al., 2016; de Lau and Breteler, 2006; Di Monte et al., 2002*).

Table 3. Environmental factors of PD

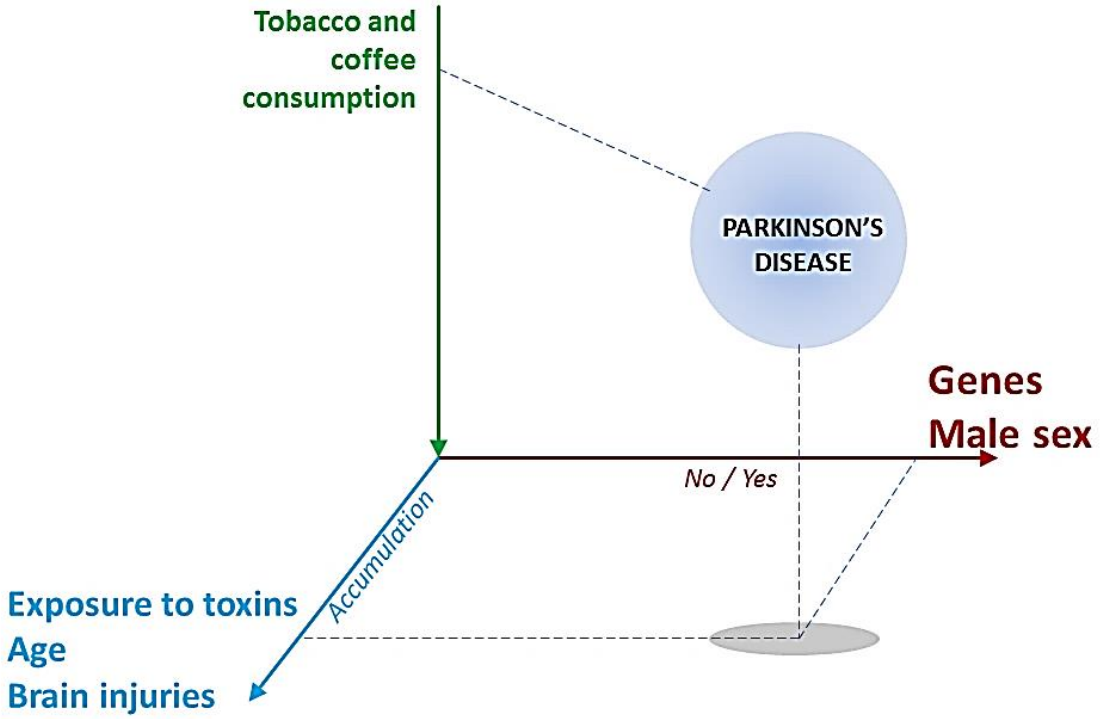
Factor	Reference
Exposure to pesticides (e.g. rotenone, dieldrin)	Tanner et al., 2011; Kanthasamy et al., 2008
Exposure to heavy metals (manganese, iron, copper)	Kwakye et al., 2015; Willis et al., 2010
Exposure to solvents (e.g. trichloroethylene)	Goldman et al., 2012
Rural living and farming activity	Kab et al., 2017; Moisan et al., 2011
Neurotoxin MPPT	Langston et al., 1999
Methamphetamine	Curtin et al., 2015
Traumatic head injury	Ha et al., 2016
Stress and depression	Hemmerle et al., 2012
Lower uric acid serum level	Wen et al., 2017
Lower vitamin D serum level	Rimmelzwaan et al., 2016

Potential protective factors

Certain environmental factors are referred to as *neuroprotective agents*, because data from the epidemiological studies showed decreased incidence of PD in the presence of such factors. Neuroprotective factors include: tobacco consumption (*Li et al., 2015*), and coffee consumption (*Costa et al., 2010*). Less confident association was found between decreased risk of PD and alcohol consumption (*Bettiol et al., 2015*) and nonsteroidal anti-inflammatory drug ibuprofen (*Ascherio and Schwarzschild, 2016*).

In conclusion, the exact aetiology of PD in the majority of individuals remains unknown, but both genetic and environmental factors may contribute (*Fig. 2*). Additionally, there is growing evidence that epigenetics may provide a comprehensive answer to the problem of aetiology of PD. Some researchers suggested a unifying understanding of how different causes of PD relate one to one another (*McNaught et al., 2001*; *Wong and Krainc, 2017*), hypothesising that dysfunctions of protein degradation might be an important factor in the degenerative processes that occur in the various aetiological forms of PD.

Figure 2. Possible interplay between aetiological factors of PD



The presence of risk genes and male sex, brain injuries, ageing and exposure to toxins increase the risk of having PD, while tobacco and coffee consumtion was found to be associated with a lower risk of PD.

Pathophysiology of Parkinson's disease

The pathological diagnosis of PD is characterized by two cardinal morphopathological findings: death of dopaminergic neurons, located in basal ganglia (namely in *pars compacta* of *substantia nigra*), and abnormal cytoplasmatic aggregates of proteins called *Lewy bodies,* located in the the surviving neurons. A major protein of Lewy bodies is an abnormally modified form of alpha–synuclein (SNCA), which is normally located in presinaptical regions of neurons. The exact mechanism of this neuronal death is not resolved and several theories are proposed (*Tansey and Goldberg, 2010*). Some of these include:

a) disfunction of alpha–synuclein metabolism, which leads to its fibrillization and aggregation and staged dissemination in the brain (*Braak et al., 2003*);
b) disruption of autophagy mechanism (*Ghavami et al., 2014*);
c) disruption of mitochondrial function (*Chen and Chan, 2009*);
d) microglial inflammation (*Glass et al., 2010*);
e) neurovascular disfunction (*Zlokovic, 2011*);

Importantly, there is a clear evidence, that the pathophysiology of PD is not limited to dopaminergic neurons of substantia nigra, but implicates a *distributed brain network*: putamen, striatum, thalamus, brainstem, and cortex (*Galvan and Wichmann, 2008*).

Cognitive decline in Parkinson's disease

As discussed above, cognitive impairment is an important non-motor symptom in PD and has a considerable impact on functioning, quality of life, caregiver burden, and health-

related costs (*Svenningson et al., 2012*). Cognitive deficits are present throughout the whole course of PD, from initial to advanced stages (*Pagonabarraga and Kulisevsky, 2012*). The profile and incidence of cognitive decline vary a lot among PD patients (*Aarsland et al., 2017*). The spectrum of PD related cognitive decline includes three syndromes of various severity (from mild to severe): subjective cognitive decline (SCD), mild cognitive impairment (PD-MCI), and PD-D. Subjective cognitive decline gained research interest during the recent years; in this syndrome, no clinical evidence (normal cognitive test performance) of cognitive deficits is found, but such deficits are noted by patients themselves or family members and caregivers. Currently, no consensus criteria for SCD exist, but many researchers report SCD in PD patients as a harbinger of future cognitive deterioration (*Erro et al., 2014*). In PD-MCI, cognitive deficits are identified by cognitive test performance, but these deficits do not impair daily life of the patient (i.e. socail and professional activity), independently of the impairment caused by motor or other than cognitive features of PD (*Litvan et al., 2012*). Finally, cognitive deficits in PD-D are severe enough to impact daily life and independence of patients (*Emre et al., 2007*).

However, the aforementioned cognitive syndromes are consecutive, and nearly all patients will be affected over time, thus the separation between the stages of cognitive deterioration in PD – normal cognition, SCD, PD-MCI and PD-D – is not strict and significantly varies depending on the applied criteria and cognitive measurement procedures utilized (*Aarsland et al., 2017*).

Dementia (severe cognitive disorder) in Parkinson's disease

Several studies have shown that the point prevalence of dementia in patients with PD is about 30%, and that the incidence rate of dementia in PD is 4 – 6 times higher than in healthy subjects (*Aarsland et al., 2005a; Riedel et al., 2008; Kim et al., 2009*). The cumulative prevalence of dementia in patients with PD ranges from 5.4% to 19.2% after five years[9] (after diagnosis of PD) (*Santangelo et al., 2015; Pedersen et al., 2013*), to 46% after ten years (*Williams-Gray et al., 2013*), and 83% after surviving more than twenty years (*Hely et al., 2008*). PD-D is associated with a twofold increase in mortality (*Levy et al., 2002*), increased caregiver strain (*Aarsland et al., 2007a*) and increased healthcare costs (*Vossius et al., 2011*).

Diagnostics of dementia in Parkinson's disease

Before 2007, no specific diagnostic criteria for PD-D existed. A diagnosis of PD-D was set up on the grounds of generic neuropsychiatric criteria, i.e. according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV; *American Psychiatric Association, 1994*). The specifically aimed diagnostic criteria for PD-D were defined in the guidelines of the International Parkinson and Movement Disorders Society (MDS; *Emre et al., 2007*). The core defining feature of PD-D in these guidelines is the emergence of dementia in the setting of established PD (*Panel 1*). Dementia is defined as a syndrome of insidious onset and progressive decline of cognition and functional capacity from a premorbid level, that is not attributable to motor or autonomic symptoms. The guidelines

[9] Discrepancies in results between studies are likely to be explained by differences in case selection, use of different criteria for PD-MCI and PD-D, and loss to follow-up (*Aarsland et al., 2017*).

with neuropsychological assessment methods to be carried out with patients with suspection to PD-D were published by the same workgroup (*Dubois et al., 2007*).

Panel 1. MDS diagnostics guidelines for PD-D (from Emre et al., 2007)

I. Core features

1. Diagnosis of PD according to Queen Square Brain Bank criteria (*Hughes et al., 1992*);
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established PD and diagnosed by history, clinical, and mental examination, defined as:
   - *Impairment in more than one cognitive domain;*
   - *Representing a decline from premorbid level;*
   - *Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.*

II. Associated clinical features

1. Cognitive features:
   - *Attention: impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day;*
   - *Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)*;
   - *Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction;*
   - *Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall;*
   - *Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present;*
2. Behavioral features:
   - *Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior;*
   - *Changes in personality and mood including depressive features and anxiety;*
   - *Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects;*
   - *Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions;*
   - *Excessive daytime sleepiness.*

III. Features which do not exclude PD-D, but make the diagnosis uncertain

1. Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging;
2. Time interval between the development of motor and cognitive symptoms not known.

IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PD-D

1. Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:
   - *Acute confusion due to*
     a) Systemic diseases or abnormalities
     b) Drug intoxication
   - *Major Depression according to DSM IV*
2. Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN[10] (*Erkinjuntti, 1994*) (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant

[10] NINDS-AIREN - National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences

cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Distinction between dementia in Parkinson's disease and dementia with Lewy bodies

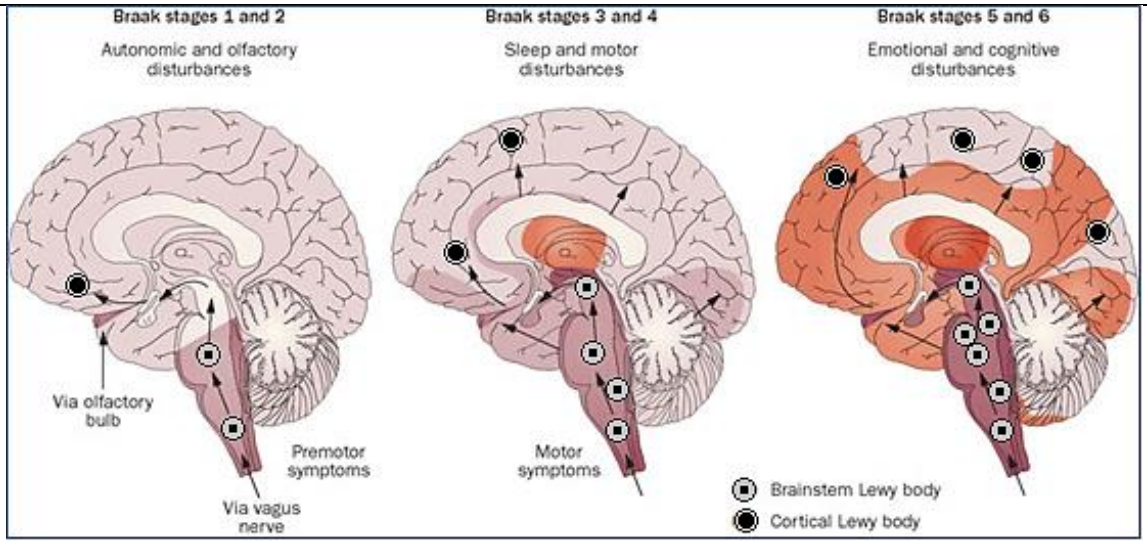
Clinical, neuropsychological and neuropathological features of PD-D overlap with those of *dementia with Lewy bodies* (DLB). Currently, DLB is recognized as distinct nosological entity, a type of dementia which rapidly progresses over time. The distinguishing clinical and pathological features of DLB are presence of Lewy bodies in neurons of the cerebral cortex (unlike the «classic» Lewy bodies of PD, which are found in basal ganglia) and very rapid progression to cognitive decline after the onset of parkinsonian-type motor impairment. Additionally, dementia in case of DLB is characterized with fluctuating cognition with pronounced variation in attention and alertness, recurrent visual hallucinations, severe neuroleptic sensitivity, and association with REM sleep behavior disorder (*Mrak and Griffin, 2007*). In the criteria of DLB consortium the distinction between PD-D and DLB is made solely on the temporal sequence of cognitive symptoms to motor onset (*McKeith et al., 2005*). Those patients who develop cognitive impairment within one year after motor onset (or prior to motor symptoms) are classified as DLB, and those patients, who develop cognitive impairment after longer than one year after motor onset, are classified as PD-D («*one year rule*»). However, in the revised MDS criteria for PD (2015), a DLB subtype of PD was introduced to define cases with rapid progression to dementia regardless the timing of cognitive impairment to motor impairment (*Postuma et al., 2015*). Thus, the distinction between PD-D and DLB is blurred and requires further exploration. The overlap in symptoms and other evidence suggest that DLB and PD-D (and PD *per se*) may be linked to the same underlying abnormalities of alpha–synuclein. A generic term "*Lewy body disease*" is used to encompass both DLB and PD-D (*Brenowitz et al., 2017*).

Pathophysiology of dementia in Parkinson's disease

The pathophysiology of PD-D is not yet fully understood. There is a number of theories explaining cognitive deterioration within PD. In most of such theories, the emergence of cognitive deficits is related to neurodegenerative process. Potential factors contributing to PD-D encounter Lewy bodies, α-synuclein interactions, beta-amyloid aggregates, and neurotransmitter dysfunction.

Some researchers postulated that the accumulation of Lewy bodies in the limbic system and cortex is the main substrate of cognitive decline in PD (*Apaydin et al., 2002; Aarsland et al., 2005b*). According to Braak hypothesis (*Braak et al., 2004, 2005*), PD-D emerges when Lewy body pathology spreads to the limbic and cortical regions (this corresponds to Braak stages 5 and 6, figure 3).

Figure 3. The Braak staging system of Parkinson disease



The Braak staging system of Parkinson disease, showing the initiation sites in the olfactory bulb and the medulla oblongata, through to the later infiltration of Lewy pathology into cortical regions.
α-Synuclein-related pathology is possibly initiated in the periphery via input from the olfactory epithelium or vagal inputs from the stomach, perhaps involving xenobiotic factors. The red shading represents the pattern of pathology.
With permission from John Wiley and Sons (source: Halliday et al., 2011).

Kramer and Schulz-Schaeffer (2007) demonstrated that PD-D is related to the damage of synapses caused by pre-synaptic α-synuclein. Other researchers pointed out to the importance of beta-amyloid aggregation (*Halliday and McCann, 2010; Compta et al., 2011*). And some other publications highlighted the influence of neurotransmitter systems dysfunction in the development of PD-D, i.e. cholinergic (*Calabresi et al., 2006; Jellinger, 2006; Bohnen and Albin, 2011a*), noradrenergic and serotonergic (*Cirrito et al., 2011; Kotagal et al., 2012*).

In conclusion, the pathophysiological process behind PD-D is heterogeneous and multifactorial as PD itself. Better understanding the mechanism of cognitive deterioration in PD is warranted and will significantly contribute to prediction and treatment in the future.

Deep brain stimulation and dementia in Parkinson's disease

As discussed in Chapter 1, DBS is a surgical implantation of an electrical pulse generator with electrodes projected to specific targets in the brain. DBS has provided satisfactory therapeutic benefits for some neurological and psychatric disorders resistant to conservative treatment: i.e. PD, essential tremor, dystonia, and depression (*Kringelbach et al., 2007*). In recent years, it has been largely acknowledged that DBS can alleviate motor symptoms of PD, though the exact mechanisms of therapeutic effects of DBS are still not fully resolved (*Garcia et al., 2013*).

Two surgical targets are considered the most common procedures for DBS in PD: subthalamic nucleus and globus pallidus internus (GPi). Proponents of GPi-DBS, mostly in the North America, consider that targeting GPi causes less behavioural side-effects, being equally effective (*Hariz, 2017; Williams et al., 2014*). Cognitive impairment in PD is a limiting factor for the selection of candidates for DBS, also evidence has been

accumulating regarding changes in cognitive performance after DBS itself (*Massano and Garett, 2012*).

In a comparative meta-analysis of STN-DBS vs. GPi-DBS in terms of cognitive and psychiatric effects it was found that STN-DBS was associated with a decline in global cognition, attention, working memory, verbal fluency, and memory ; however, there were no differences in terms of quality of life and psychiatric effects (*Wang et al., 2016*).

In a meta-analysis of 10 controlled studies of DBS to the subthalamic nuclei, an association with postoperative decline in global cognition, memory, phonemic fluency, semantic fluency, and executive function was found (*Xie et al., 2016*).

Biomarkers of dementia in Parkinson's disease

The term "biomarker"[11] refers to a broad category of medical signs which can be measured accurately and reproducibly (*Strimbu and Tavel, 2010*). A more specific definition refers to biomarker as "*any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease*" (*WHO, 2001*). *Amur et al. (2015)* suggested to classify biomarkers in the following four types: 1) **diagnostic** - these distinguish between patients with a pathological condition and healthy patients; 2) **prognostic** – these provide information on the possible course of untreated disease, in other words, prognostic biomarkers inform about the severity of the disease in the absence of treatment; 3) **predictive** – these provide information on the possible course of a treated disease, in other words predictive biomarkers inform about the potential for a patient to respond (favorably or not) to a treatment; 4) **response** - these are dynamic assessments in the course of a treatment, which identify a presence of a biological response to a therapeutic intervention. With regard to the focus of the present dissertation, we are searching for **prognostic biomarkers**, i.e. parameters which provide information on the likely course of cognitive decline in PD. There are many biomarkers that have been proposed as possible candidates for the development of PD-D; these cover various clinical and technological modalities (Tables 4.1-3). Evidence has shown that certain clinical factors are associated with higher risk of cognitive decline in PD (Table 4.1).

Table 4.1. Potential clinical biomarkers of PD-D

Factor	**Marker**	**Reference**[12]
Age	advance of age, particularly age over 70	Aarlsland et al., 2007b
Sex	males	Levy et al., 2000
Education	low educational level	Levy et al., 2000
Neuropsychological tasks performance	poor performance in tests that involve more posterior cortical function (i.e. verbal fluency)	Williams-Gray et al., 2007
Visual hallucinations	presence	Galvin et al., 2006
Rapid-eye-movement sleep behavior disorder	presence	Boot et al., 2012
Olfactory dysfunction	decrease of olfaction	Baba et al., 2012

[11] Portmanteau of "biological marker"

[12] Full list of references for each factor is not provided

Blood pressure	high baseline blood pressure and orthostatic blood pressure drop	Anang et al., 2014
Color visions	abnormal color visions	Anang et al., 2014
Gait	baseline gait dysfunction	Anang et al., 2014

Neuroimaging methods used to predict PD-D have included both structural and functional techniques (Table 4.2). Structural methods are based on the assessment of cortical atrophy in temporal, parietal and occipital cortices, hippocampus and amygdala, and on the assessment of white matter changes. Functional methods are focused on the assessment of regional hypoperfusion, glucose metabolism and neurotransmitter activity.

Table 4.2. Potential neuroimaging biomarkers of PD-D

Modality	**Method**	**Marker**	**Reference[13]**
Magnetic resonance imaging	voxel-based morphometry	atrophy in temporal, parietal and occipital cortices	Weintraub et al., 2011; Melzer et al., 2012
	region of interest	reduced hippocampal and amygdala volumes	Compta et al., 2012; Bouchard et al., 2008
	cortical-thickness analysis	cortical thickness in the anterior temporal, dorsolateral prefrontal, posterior cingulate, temporal fusiform and occipitotemporal cortex	Zarei et al., 2013
	white matter lesions	white matter hyperintensities	Lee et al., 2010
	diffusion tensor imaging	bilateral parietal white matter changes	Hattori et al., 2012
	arterial spin labelling	regional hypoperfusion in posterior cortex.	Le Heron et al., 2014
Positron emission tomography	glucose metabolism with radiotracer ^{18}F-deoxyglucose (FDG)	decreased perfusion in occipital and posterior cingulate cortices	Bohnen et al., 2011b
	acetylcholinesterase activity with radiotracer [^{11}C]PMP[14]	decreased acetylcholinesterase activity in frontal, parietal and temporal cortex	Bohnen et al., 2003
	beta-amyloid load with radiotracer Pittsburgh compound B	higher tracer retention correlated with cognitive decline	Gomperts et al., 2013

[13] Full list of references for each method is not provided

[14] 1-[11C]methylpiperidin-4-yl propionate

	tau protein load with radiotracer [^{18}F]T807	higher tracer retention in the inferior temporal gyrus and precuneus	Gomperts et al., 2016
Single-photon emission computer tomography	perfusion	hypoperfusion in bilateral posterior parietal and occipital areas	Nobili et al., 2009
	dopamine transporter density with radiotracer Ioflupane (^{123}I) (DaTSCAN)	decreased DAT in caudate nucleus	Colloby et al., 2012

Analytes of cerebrospinal fluid (CSF) showed some promising results as candidates for markers of PD-D (Table 4.3). According to a number of recent reports, patients with PD-D have lower levels of CSF amyloid beta 1-42. Investigation of concentration of α-synuclein and tau proteins (total and phosphorilated) in CSF showed less consistent results. Finally, there is some evidence that plasmatic decrease of epidermal growth factor and increase of tumor necrosis factor are associated with worse cognition in PD.

Table 4.3. Potential biological fluid markers of PD-D

Fluid	**Substance**	**Marker**	**Reference[15]**
Cerebrospinal fluid	Amyloid Beta 1-42	decreased concentration	Compta et al., 2013
	Tau	mixed results[16]	Compta et al., 2009; Siderowf et al., 2010
	α-synuclein	mixed results[17]	Stewart et al., 2014 Sako et al., 2014
Plasma	epidermal growth factor	decreased concentration	Chen-Plotkin et al., 2011
	tumor necrosis factor	increased concentration	Menza et al., 2010

Genetic and neurophysiological markers of PD-D will be discussed in Chapter 3.

Management of cognitive decline in Parkinson's disease

There is evidence of the efficacy and safety of cholinesterase inhibitors to treat severe cognitve decline in PD (*Wang et al., 2015*). Rivastigmine and donepezil were reported to have satisfactory effects in two large randomised controlled trials: respectively EXPRESS (*Emre et al., 2004*) and EDON (*Dubois et al., 2012*). Less supportive data were reported for an NMDA-receptor antagonist memantine (*Aarsland et al., 2009*). Some pharmaceutical agents are candidate-drugs for trials in PD-D, basing on theoretical and preliminary empirical evidence. Some of these are: selective monoamine oxidase B inhibitor rasagiline

[15] Full list of references for each marker is not provided;

[16] Some studies (Compta *et al. 2009*) reported an association between increased levels and cognitive impairment, but others reported no associations (Siderowf *et al., 2010*);

[17] Meta-analysis by Sako *et al., 2014*, showed decreased level of α-synuclein in PD-D, while *Stewart et al., 2014*, showed better preservation of cognitive function over time in patients with lower level of α-synuclein

(*Weintraub et al., 2016*) and selective noradrenaline reuptake inhibitor atomoxetine (*Weintraub et al., 2010*).

Some potential disease-modifying strategies (slowing the onset of PD-D) are an urgent unmet need. These include immunotherapies targeting beta-amyloid, tau-proteins and alpha‑synuclein, drugs addressing mitochondrial dysfunction, anti-inflammatory agents, GBA-active agents, stimulation of neurogenesis, and neurotrophic factors (*Aarsland et al., 2017*).

Chapter 3. Genetic and EEG markers of dementia in Parkinson's disease

Genetic markers

Genetic markers of cognitive decline in PD came in focus of the research since the discovery of the first genetic causes of PD per se. A number of genes associated with cognitive impairment in PD have been identified, however the studies yielded sometimes conflicting results (*Aarsland et al., 2017; Collins and Williams-Gray, 2016*) (Table 5).

Naturally, causal genes of PD were investigated with relation to parkinsonian non-motor symptoms, like cognitive and psychiatric impairment. Mutation in Leucine-rich repeat kinase 2 (LRRK2) gene, locus PARK8, is the most studied mutation (*Aarsland et al., 2017*). However, it showed no influence on cognition in the most of the studies, instead it even had some protective effect (*Srivatsal et al., 2015; Ben Sassi et al., 2012; Alcalay et al., 2010*). Mutations in alpha-synuclein (SNCA) gene, locus PARK1/4, also showed some association with dementia in PD (*Somme et al., 2011; Farrer et al., 2004*), however contested in one study (*Mata et al., 2014*).

Among the risk factor genes of PD, the following genes were mostly investigated: glucocerebrosidase (GBA), apolipoprotein E (APOE), microtubule-associated protein Tau (MAPT) and catechol-O-methyltransferase (COMT).

Glucocerebrosidase gene

GBA is an lysosomal enzyme of glicolipid metabolism, which is responsible for the hydrolysis of glucocerebroside (*Brady et al., 1965*). GBA showed the most significant correlation with a phenotype with severe cognitive decline (*Brockmann et al., 2014; Winder-Rhodes et al., 2013; Setó-Salvia et al., 2012*). The mechanism behind the relation of GBA mutations to PD-D is still not entirely clear. One theory proposes that impaired GBA (due to the mutation of the gene) activity of GBA enzyme and accumulation of glucocerebroside in the lysosomes acts as a backbone for alpha-synuclein aggregation in the neurons (*Mazzuli et al., 2011*).

Apolipoprotein E gene

APOE is a plasmatic protein-carrier of cholesterol, essential in lipidic metabolism in the brain (*Puglielli et al., 2003*). APOE gene is polymorphic and has three major alleles: ε2, ε3, and ε4. Whilst ε4-allele of APOE has been established as a risk factor for the development of Alzheimer's disease (AD) (*Farrer et al., 1997*), studies showed an over-representation of ε4 among cases with PD dementia (*Morley et al., 2012; Williams-Gray et al., 2009a*), showing a potential genetic overlap between PD-D and AD. However, these results were not confirmed in another study (*Kurz et al., 2009*). It is thought that the relation of ε4-allele with PD-D may be mediated (at least in part) through altered amyloid metabolism (*Gallardo et al., 2008*).

Microtubule-Associated Protein Tau gene

MAPT is a protein involved in the assembly and stabilization of axonal microtubules. The MAPT gene has two haplogroups, H1 and H2, in which the gene fragment appears in inverted orientations. Thus, a genotype may contain the following MAPT haplotype variants: H1/H1, H2/H2, and H1/H2 (*Stefansson et al., 2005*). A strong evidence on association between the MAPT gene H1/H1-haplotype and cognitive decline in PD was shown in observational studies (*Williams-Gray et al., 2009b, 2013; Setó-Salvia et al., 2011*), in another studies this association was not confirmed (*Mata et al., 2014; Morley et al., 2012*). The mechanism by which the H1 variant might cause lead to worsening of cognition in PD is unknown, but increased expression levels of total tau has been reported in PD (*Collins and Williams-Gray, 2016*).

Catechol-O-methyl Transferase gene

COMT is an enzyme which degrades catecholamine neurotransmitters (i.e. dopamine, epinephrine, and norepinephrine). COMT gene contains a functional polymorphism, which results in valine to methionine mutation at position 158 ($Val^{158}Met$) (*Schacht, 2016*). An association between alterations of executive and attention cognitive domains in PD and val-158-met-allele of COMT gene was demonstrated in some studies (*Williams-Gray et al., 2009b; Foltynie et al., 2004*). However, this genetic variant does not appear to be associated with dementia risk (*Williams-Gray et al., 2009b; Collins and Williams-Gray, 2016*).

Table 5. Genetic associations of cognitive decline in PD

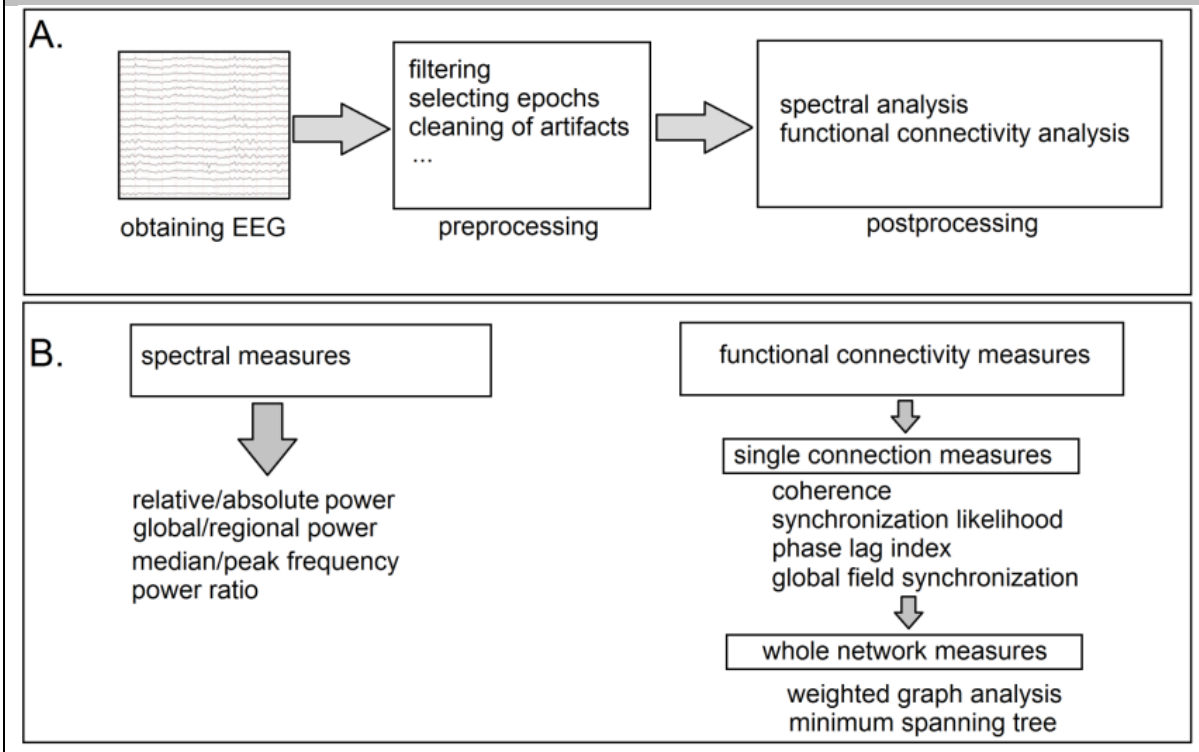
Gene	Role in the pathology of PD	Features of PD phenotype
SNCA	causal gene	early onset rapidly progressive dementia
MAPT H1/H2 hapotype	risk factor	higher dementia risk of dementia in carriers
GBA	risk factor	rapid progression to dementia
COMT val-158-met polymorphism	no proven relation	associated with altered executive and attention tasks
APOE ε4 allele	no proven relation	higher dementia risk of dementia in carriers

Quantitative EEG markers

Quantitative EEG is a mathematical processing of EEG data to extract relevant information for subsequent analysis or comparison with other kind of data (*Nuwer, 1997; Thakor and Tong 2004*). In contrast to conventional EEG, where electrical activity of the brain cells is visually analyzed, qEEG provides derivative parameters, which are generated from EEG "*raw*" data using computational methods. Quantitative EEG includes several procedural steps (Fig. 4). The first step consists of EEG signal acquisition itself - performed with the use of various EEG machines and electrode systems. Alternatively, magnetoencephalography (MEG) may be used. MEG is the recording of the magnetic fields, generated by the ionic currents at the brain cellular level; thus, both EEG and MEG are methodologically similar and relevant in neuroscience (*Lopes da Silva, 2013*). The second step includes preprocessing - eliminating the following artifacts: muscle

movements, sleepiness, eye blinks, heart beat and other types of EEG "*noise*". Preprocessing is performed by selecting "*clean*" EEG segments for analysis. The last stage is mathematical processing of the "*clean*" (artifact-free) EEG signal to extract a parameter, which denotes best the process of interest (e.g. cognitive decline). Various mathematical approaches are used for the processing; they are generally classified in linear and non-linear techniques. Linear methods are based on the concept that electric activity of the brain is a stationary process (*Al-Qazzaz et al., 2014*). Non-linear methods are based on the concept that EEG activity is a dynamic and irregular phenomenon (*Kantz and Schreiber, 2004*). Each of these methods has its advantages and disadvantages (*Netoff et al, 2006; Blinowska 2011*).

Fig. 4. Outlines of the qEEG process.

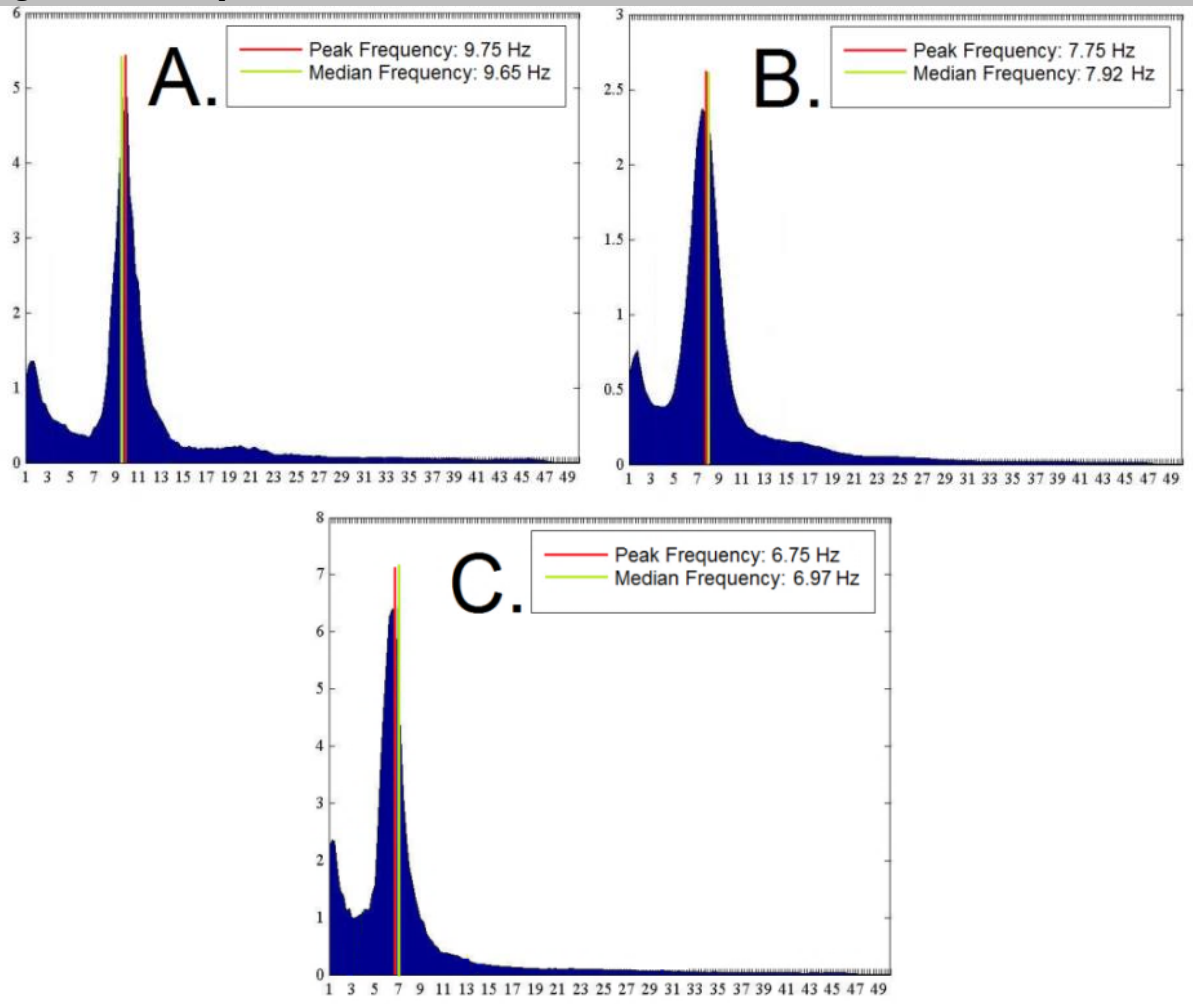


A. Main steps of the processing; B. Spectral and functional connectivity measures

Spectral analysis

Spectral analysis is a linear technique of EEG processing. It is a process by which a complex EEG signal is decomposed into its component frequencies, and the amplitude of oscillations at each frequency bin is calculated. Since oscillations around zero (like an EEG trace) would add up to 0, amplitudes are represented by their squares, called power. The totality of powers at each frequency band is called power spectrum and could be represented as a graph (Fig. 5).

Figure 5. Power spectra.



Spectra of a healthy person (A), a patient with PD-MCI (B), and a patient with PD-D (C); band power: 8-13 Hz. Images computed from the own EEG data using „TAPEEG" toolbox.

Thus, a power spectrum reflects "the amount of activity" in frequency bands. The frequency bands are the same as used in conventional EEG, generally consisting of delta (0.1-3.5 Hz), theta (4-7.5 Hz), alpha (8-13 Hz), beta (14-30 Hz), gamma (>30 Hz) (*Niedermeyer and Lopes da Silva, 2005*). However, different researchers may select slightly different frequency intervals for their analyses. Additionally, the bands could be divided into sub-bands, e.g. alpha1 (8-10 Hz) and alpha2 (10-13 Hz), for the purpose of a thorough analysis. Spectral power can be absolute or relative. Absolute power in a given frequency band, e.g. in the alpha band, corresponds to the integral of all power values as measured, while relative power is the power in a given frequency band divided by the sum of all power measurements of all frequencies. Additionally, power could be global and regional. Global power reflects the average power over the whole cortex, while regional power

characterizes the power in certain cortex regions. Mainly, five regions in each hemisphere are analyzed: frontal, temporal, parietal, occipital and central, giving a total of 10 regions.

Additionally, some average parameters of EEG frequency can be obtained in spectral analysis (*Otto 2008*). Mean frequency (also referred to as mean "power frequency" or "spectral centre of gravity") is calculated as the sum of the product of the power spectrum and the frequency divided by the total sum of the power spectrum. Median frequency is the 50% quantile of the power spectrum, in other words, it is the frequency at which the power spectrum is divided into two regions with equal amplitude. Finally, peak frequency is the frequency which corresponds to the maximum of the power spectrum.

Functional connectivity analysis

The other type of information obtained by qEEG (apart from spectral analysis) is functional brain connectivity. Functional connectivity in the context of neuronal activity may be briefly defined as a coordinated interplay between specialized brain regions (*Fingelkurts et al., 2005*). Cognitive functions (e.g. attention, memory) arise from neuronal activity, which is distributed over the brain anatomically and temporally, forming complex networks (*Palva and Palva, 2012*). These networks function on the basis of anatomical connections (white matter tracts connecting brain regions), functional connections (temporal correlations between brain regions, even anatomically unconnected), and effective connections (causal influences between networks) (*Rubinov and Sporns, 2010*). Thus, functional connectivity analysis is a measure, which enables to quantify the level of the functional connections between brain regions. As discussed by *Bosboom et al. (2009)*, when performing connectivity analyses, we assume that two dynamically active neural networks are designated "A" and "B". Time series "ai" and "bi", using EEG signals from both networks, are recorded. The main purpose is to analyze the functional relation between "A" and "B" from "ai" and "bi" and to quantify the level of this relation. This quantification is performed with both linear and non-linear methods. Linear approaches in connectivity analysis assumes that the more "ai" and "bi" corresponds to each other, the stronger is the relation between "A" and "B". In this way, for instance, the coherence is calculated as an estimate of a function of frequency between two signals (*Schoffelen and Gross 2009*). In contrast to coherence, where the stability of the phase relation between two signals is assessed and taken as an indicator of synchronization between the brain regions, the global field synchronization (GFS) makes no assumption about the spatial location of the activity (*Koenig et al., 2001*, *2005*). GFS is calculated as a function of all frequency bands.

However, there can be a functional relation between the structures "A" and "B" even if time series "ai" and "bi" do not correspond to each other; in this case non-linear methods of analysis are applied. One of these methods is synchronization analysis, which implies that "the state of A is a function of the state of B" (*Stam et al., 2007*). Synchronization Likelihood (SL) is an estimate of synchronization, which reflects dynamic interactions of the chaotically active coupled networks. SL denotes how strongly a signal channel at a given time is synchronized to other channels. Another estimate of synchronization is Phase Lag Index (PLI). PLI is calculated from the asymmetry of the distribution of

instantaneous signal phase differences between two brain regions and has the advantage of being free of effects of volume conduction as opposed to the methods mentioned before. In other words, PLI reflects the degree of synchronization between couples of signals.

After characterization of single connections, the next level of connectivity analysis consists in description of the whole network, applying graph theory method. In this method functional connections between brain structures are described as graphs (networks) (*Watts and Strogatz 1998*). These graphs consist of vertices (nodes) and corresponding sets of edges (connections). There are different approaches to assess the obtained graph: e.g. weighted graph analysis and minimum spanning tree. The two fundamental measures of weighted graph are: Clustering Coefficient (CC) and Path Length (PL). *Olde Dubbelink et al., (2014b)* describe CC as an estimate of "the likelihood that neighbors of a vertex are also connected to each other, and characterizes the tendency to form local clusters". In other words CC describes local "connectedness". The same author described PL as a "measure for global integration of the network. It is defined as the harmonic mean between all possible vertex pairs in the network, where the shortest path between two vertices is defined as the path with the largest total weight". Thus PL describes global "connectedness".

Graphs may be very complex and large, forming a variety of nodes and paths. A subgraph can be developed which connects all nodes through the shortest paths without forming cycles; such subgraph is referred to as minimum spanning tree of a weighted graph (*Stam et al., 2014*). The following measures are used for minimum spanning tree estimation: leaf number (the number of nodes with only one edge), eccentricity of a node (the length of the longest connection from this node to any other node), betweenness centrality of a node (the fraction of all connections in the tree that include, but do not stop at, that node), and tree hierarchy (a quotient of the leaf number to the product of twice the number of edges to the highest betweenness centrality of any node in the tree). These measures estimate the complexity of connections in the topographical brain network.

Reliability of the qEEG analysis: individual variability

According to *Näpflin et al. (2007)* inter-individual variability of absolute power of the traditional frequency bands in healthy humans is large, while intra-individually the power spectrum remains stable over a period of 12 to 40 months in healthy individuals. However, interpretation of a change in relative power in an individual is ambiguous and requires knowledge of more information than a change in absolute power. For example a decrease of the relative alpha power can be due to either a decrease of absolute alpha power but also to an increase of the absolute power in one or more of the other frequency bands without any change in the absolute alpha power, or to a combination of both. In cross-sectional comparisons of small groups of individuals, alterations in relative power are more easily detected than changes in absolute power, while absolute power is a good measure for longitudinal, intra-individual changes or cross-sectional comparisons of very large populations. Derived indices were proposed as a possible solution for the problem that exists in relative power relationship between frequency bands: spectral ratio (sum

of alpha and beta powers divided by the sum of delta and theta powers) (*Morita et al., 2011*), or alpha/theta ratio (*Gu et al., 2016*).

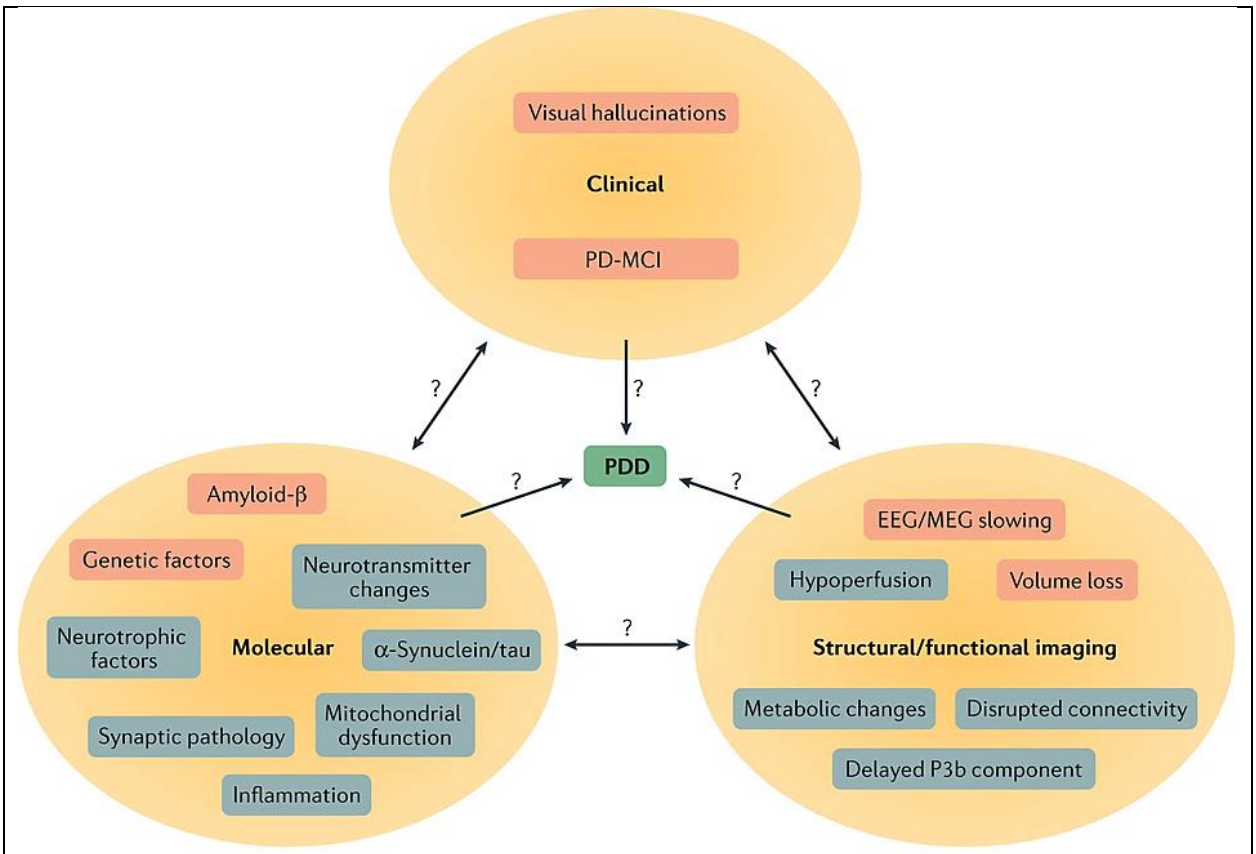
Test-retest effect

According to consecutive reports EEG frequency parameters are stable over time. *Gasser et al., (1985)* were amongst the first to address the issue of test-retest reliability of qEEG parameters. They reported that alpha electrical activity of the brain cortex showed the best reliability and delta and beta activity had the worst reliability. *Dustman et al., (1999)* investigated the variability of absolute and relative powers in five frequency bands – delta, theta, alpha, beta, and gamma – over the interval of 6 months in a sample of 222 males aged from 4 to 90 years. Age-related dependence of the parameters was identified, but the frequency markers, especially power in the alpha band, showed a satisfactory reliability over time. Later, *Näpflin et al., (2007)*, in above mentioned study, replicated these results in healthy adults. Additionally, the qEEG frequency markers are not influenced by cognitive activity. *Grandy et al., (2013)* investigated the modifiability of the alpha frequency of healthy subjects before and after a series sessions of cognitive tasks. Cognitive tasks had no significant effects on the resting state peak alpha frequency 7.5 – 12.5 Hz.

Influence of dopamine-replacement therapy on qEEG parameters

The effects of levodopa and dopaminergic medication on the EEG activity of the patients yielded ambiguous results: while some researchers reported that patients in a medicated and a non-medicated state revealed no influence of dopamine-replacement therapy on frequency characteristics (*Stoffers et al., 2007; Moazami-Goudarzi et al., 2008*), various other studies reported that levodopa treatment of PD induces an increase in alpha and beta bands, and a decrease of theta and delta bands. These latter changes are referred to as "activation" of EEG (*Gironell et al., 1997*). *George et al. (2013)* analyzed the EEG power spectra and connectivity in non-demented PD patients in ON- and OFF-medication state, in both resting state and during a cognitive task. These results were compared to those of a group of healthy controls. No significant changes in powers were identified in relation to medication. Despite that fact, the authors showed that dopaminergic medication reduced the pathological synchronization in the beta band in the resting state, and induced task-related increase of beta power. These findings were consistent with the previous reports (*Brown 2007; Stoffers et al., 2008*). According to other researchers levodopa treatment has influence on functional brain connectivity assessed by MEG and these changes were mostly identified in beta frequency range. (*Stam 2010*). Therefore, studies of beta activity require adjustments according to dopaminergic stimulation while data with alpha and theta activity is probably largely independent from dopaminergic influence.

Figure 6. Overview of risk factors for Parkinson disease dementia.



Three different categories of risk factors for Parkinson disease dementia (PDD) — clinical, molecular, and structural/functional imaging — are illustrated. Factors with evidence from longitudinal studies are shaded pink, and factors with evidence from cross-sectional studies are shaded grey. Interrelationships between factor categories (bidirectional arrows) and temporal relationships between cross-sectional factors and PDD (unidirectional arrows) remain unclear. MCI, mild cognitive impairment; MEG, magnetoencephalogram. With permission from Nature Publishing Group (source: Aarsland et al, 2017)

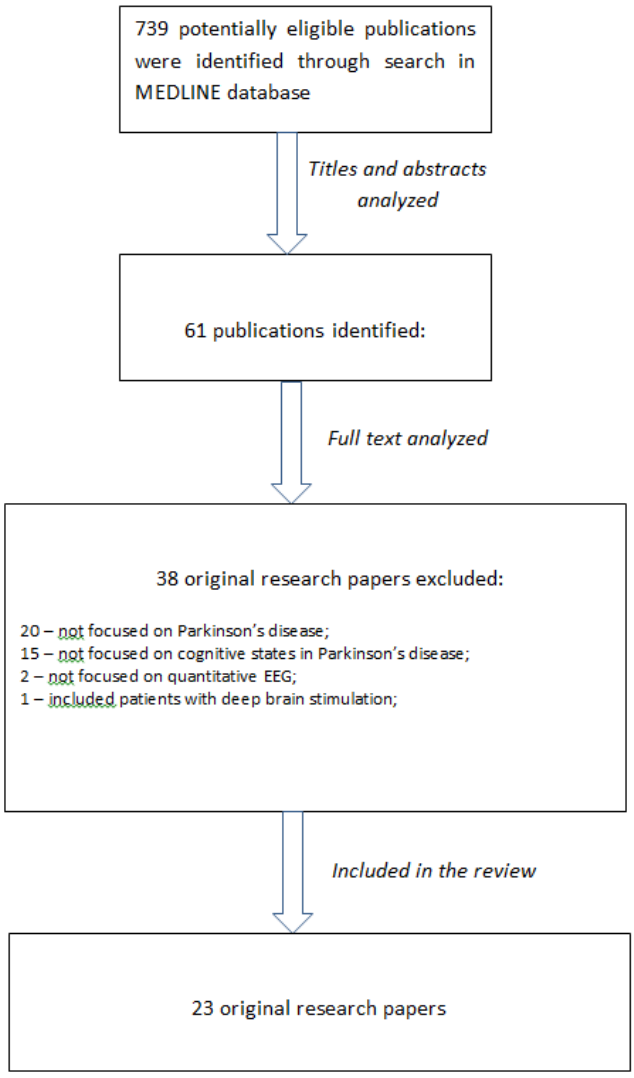
Chapter 4. Quantitative EEG markers of dementia in Parkinson's disease (systematic review)

As discussed in Chapter 3, quantitative EEG has shown good potential in identification of cognitive deterioration in patients with PD. Quantitative EEG is advancing fast, and various new methods have been introduced and applied in qEEG research. In this review, we analyzed recent publications addressing its predictive value for detecting of PD related worsening of cognition.

Methods of literature search

References for this review were identified through search of the MEDLINE database (Panel 2). The following search strategy was used: *((((eeg) AND parkin*))) AND ("2005"[Date - Publication]: "2015"[Date - Publication])*. 739 potentially eligible publications were identified with this search query on March 2nd 2015.

Panel 2. Selection of the publications



The titles and abstracts were examined for selection criteria:

a) *full text available in English;*
b) *original research studies;*
c) *subjects of the study: patients with PD, who were assessed by qEEG (spectral or/and connectivity analysis) and had not undergone deep brain stimulation;*
d) *qEEG variables acquired through conventional EEG machines or MEG in resting state eyes-closed conditions in "ON" or/and "OFF" levodopa medication condition;*
e) *studies focusing on comparison between groups of PD patients with different states of cognition (e.g. PD-D vs. PD-MCI) or/and longitudinal qEEG evaluations of cognition in patients with PD or/and evaluations of correlation of qEEG variables with tests and tools for cognitive assessment.*

Sixty one papers original research papers were identified after analysis of the titles and abstracts, and subject to full text analysis. After analysis of the full text, 24 original research publications in peer-reviewed journals were selected for the final analysis (Table 6).

Analysis of the findings

These studies were performed by ten independent research groups. Independence of the authors was analyzed by reviewing the affiliations of the first and the corresponding authors. Details summarizing the profiles of the included publications are shown in Table 6. Profiles of the excluded papers are shown in Supplement 1.

Table 6. Profiles of the studies, which met the inclusion criteria.
AD – Alzheimer's disease; DLB – dementia with Lewy bodies; HC – healthy controls; PD-D – Parkinson's disease with dementia; PD-MCI– Parkinson's disease with mild cognitive impairment; PDNC - Parkinson's disease with normal cognition; PDwD – Parkinson's disease without dementia (no information on MCI).

No	Author(s)	Type of the study/setting;	Analyzed parameter(s)	Affiliation of the corresponding author
Studies with EEG with 10-20 international system				
1	Caviness et al. 2007	comparison of 8 PD-D vs.16 PD-MCI vs. 42 PDNC	Relative spectral power	Mayo Clinic, Scottsdale, USA
2	Bonnani et al. 2008	observation of 36 LBD, 19 PD-D without cognitive fluctuations, 16 PD-D with cognitive fluctuations, 17 AD and 50 HC	Compressed spectral arrays and relative spectral power	University G. d'Annunzio of Chieti-Pescara, Pescara, Italy
3	Fonseca et al. 2009	comparison of 7 PD-D vs. 10 PD-MCI vs. 15 PDNC vs. 26 HC	Relative and absolute amplitudes	Pontificia Universidade Catolica de Campinas, Campinas, Brazil
4	Kamei et al. 2010	comparison of PD patients with executive dysfunction vs. 25 PD patients without executive dysfunction.	Absolute spectral power	Nihon University School of Medicine, Tokyo, Japan
5	Babiloni et al. 2011	comparison of 13 PD-D vs. 20 AD vs. 20 HC	Spectral and source analyses	Casa di Cura San Raffaele Cassino, Italy
6	Klassen et al. 2011	observation of 106 PD-wD	Relative spectral power	Mayo Clinic, Scottsdale, USA

7	Morita et al. 2011	comparison of 100 PD: 43 with MMSE 28-30 vs. 35 with MMSE 24-27 vs. 22 with MMSE <24	Absolute spectral power	Nihon University School of Medicine, Tokyo, Japan
8	Pugnetti et al. 2010	comparison of 21 PDwD vs. 7 PD-D vs. 10 LBD vs. 14 HC.	Global field synchronization	Scientific Institute S. Maria Nascente, Milan, Italy
9	Fonseca et al. 2013	comparison of 12 PD-D vs.31 PDwD vs. 38 AD vs. 37 HC	Absolute spectral power and coherence	Pontificia Universidade Catolica de Campinas, Campinas, Brazil
10	Gu et al. 2016	observation of 9 PD-D and 17 PD-MCI	Relative and absolute spectral power	Nanfang Hospital, Guangzhou, China
11	Caviness et al. 2015	observation of 71 PDwD	Relative spectral power	Mayo Clinic, Scottsdale, USA
12	Fonseca et al. 2015	comparison of 31 PDwD vs. 28 AD vs. 27HC	Absolute spectral power and coherence	Pontificia Universidade Catolica de Campinas, Campinas, Brazil
Studies with EEG with 256 channels				
13	Benz et al. 2014	comparison of 20 PD-MCI vs. 20 PD-D vs. 20 AD vs. 20 HC	Relative spectral power	Hospitals of the University of Basel, Basel, Switzerland
14	Bousleiman et al. 2014	comparison of 12 PDNC vs. 41 PD-MCI	Relative spectral power	Hospitals of the University of Basel, Basel, Switzerland
15	Zimmermann et al. 2015	analysis of 48 PDwD	Median background frequency	Hospitals of the University of Basel, Basel, Switzerland
Studies with 151-channel whole-head MEG				
16	Bosboom et al. 2006	comparison of 13 PD-D vs. 13 PDwD vs. 13 HC	Relative spectral power	VU University Medical Center, Amsterdam, the Netherlands
17	Stoffers et al. 2007	comparison of 70 PDwD vs. 21 HC	Relative spectral power	VU University Medical Center, Amsterdam, the Netherlands
18	Stoffers et al. 2008	comparison of 70 PDwD vs. 21 HC	Synchronization likelihood	VU University Medical Center, Amsterdam, the Netherlands
19	Bosboom et al. 2009	comparison of 13 PD-D vs. 13 PDwD	Synchronization likelihood	VU University Medical Center, Amsterdam, the Netherlands
20	Ponsen et al. 2013	comparison of 13 PD-D vs. 13 PDwD	Relative spectral power and phase lag index	VU University Medical Center, Amsterdam, the Netherlands

21	Olde Dubbelink et al. 2013a	observation of 49 PDwD and 14 HC	Relative spectral power	VU University Medical Center, Amsterdam, the Netherlands
22	Olde Dubbelink et al. 2013b	observation of 43 PDwD and 14 HC	Phase lag index	VU University Medical Center, Amsterdam, the Netherlands
23	Olde Dubbelink et al. 2014b	observation; 63 PDwD	Weighted graph and minimum spanning tree	VU University Medical Center, Amsterdam, the Netherlands
24	Olde Dubbelink et al. 2014a	observation of 43 PDwD and 14 HC	Relative spectral power	VU University Medical Center, Amsterdam, the Netherlands

In spite of a common concept – applying qEEG methods to investigate cognition of patients with PD – these studies were too heterogeneous in terms of applied methods. The researchers use different methods of mathematical processing of the EEG, different approaches (such as spectral or connectivity analysis), and different settings. While there is a more or less common consensus regarding diagnostic criteria of an advanced cognitive deterioration – PD-D, such a consensus regarding diagnostic criteria for intermediate (between normal cognition and PD-D) cognitive disorder – mild cognitive impairment – is still under discussion (*Winblad et al., 2004; Palmer and WInblad, 2007; Ganguli et al., 2011*). Due to these differences a full meta-analysis was not performed. However, the effect sizes of the reported variables were calculated in order to compare the relevant results. The *effect size* is a statistical measure, reflecting how much two standardized means are different between two populations (*Kelley and Preacher, 2012*). The larger the effect size is, the more two populations are distinct in a studied parameter. Similarly, correlation coefficients were analyzed by *Fisher's Z transformation* (*Cox, 2008*). In this case, the larger the Fisher's Z is, the stronger is the correlation.

Spectral characteristics of cognitive states in Parkinson's disease

Global power spectra

Seventeen studies focused on spectral features of cognitive states in PD. Six of these 17 studies focused on the capacity of discrimination between better and worse states of cognition in PD (e.g. group of patients with PD-MCI vs. group with PD patients with normal cognition (PDNC); or group with PD-MCI vs. group with PD-D) (Table 7). Global delta and theta powers (these variables were increased in PD-D patients) and peak background frequency (decreased in PD-D patients) had the largest effect sizes to discriminate PDNC vs. PD-D. Global delta power (increased in PD-D patients), peak background frequency and global alpha power (decreased in PD-D patients) had the largest effect sizes to distinguish PD-MCI vs. PD-D. Additionally, beta peak frequency was significantly increased ($p<0.01$), and global alpha power and alpha/theta ratio were significantly decreased ($p<0.01$ and $p<0.01$) in PD-D vs. PD-MCI in one report (although original data

was not available) (*Gu et al., 2016*). Global alpha power, peak background frequency (decreased in PD-MCI patients) and global theta power (increased in PD-MCI patients) had the largest effect sizes to discriminate PDNC vs. PD-MCI.

Table 7. EEG and MEG spectral markers which significantly discriminate between cognitive states in PD

[1] original data not available, effect size and confidence intervals estimated using p value conversion;
[2] the study is longitudinal; only assessment on admission is shown in this table;
[3] age for groups of the patients not available, age of the combined sample is shown;
[4] mean age not available, mean age calculated from median and range according to Hozo et al., 2005

CAF – Clinical Assessment of Fluctuations; DF – dominant frequency; DFV – dominant frequency variability;DSM-IV - Diagnostic and Statistical Manual of Mental Disorders IV; GRP – global relative power; MCI – mild cognitive impairment; PD – Parkinson's disease; PDNC – Parkinson's disease without cognitive impairment; PD-MCI – Parkinson's disease with mild cognitive impairment; PD-D – Parkinson's disease with dementia; PDwD – Parkinson's disease without dementia; PD-DnF – Parkinson's disease with dementia without cognitive fluctuations; PD-DF - Parkinson's disease with dementia with cognitive fluctuations.

Author(s)	Diagnostic groups of patients with PD (N)	Mean age (years)	Evaluative tests: cognitive pathology (criteria)	Parameter(s) showed significant difference between the groups with PD	Effect size (95% CI)
Bosboom et al. 2006	PD-D (13) PDwD (13)	74.4 71.7	Dementia (DSM-IV)	GRP delta (0.5-4 Hz) and GRP theta (4-8 Hz)[1]	PDwD vs. PD-D 1.47 (0.60, 2.34)
				GRP alpha (8-13 Hz) and GRP beta (13-30 Hz)[1]	PDwD vs. PD-D -1.47 (-2.34, -0.60)
				GRP gamma (30-48 Hz)[1]	PDwD vs. PD-D -1.47 (-2.34, -0.60)
Caviness et al. 2007	PD-D (8) PD-MCI (16) PDNC (42)	78.0 80.4 74.6	Dementia (DSM-IV); MCI (*Petersen et al. 1999*)	GRP delta (1.5-3.9 Hz)	PDNC vs. PD-MCI 0.11 (-0.47, 0.68) PD-MCI vs. PD-D 1.27 (0.35, 2.19) PDNC vs. PD-D 1.46 (0.67, 2.29)
				GRP theta (4-7.9 Hz)	PDNC vs. PD-MCI 0.75 (0.16, 1.34) PD-MCI vs. PD-D 0.38 (-0.46, 1.24) PDNC vs. PD-D 1.37 (0.57, 2.17)
				GRP alpha (8-12.9 Hz)	PD-MCI vs. PD-D -0.86 (-1.75, 0.01) PDNC vs. PD-D -1.01 (-1.79, -0.22)
				GRP beta1 (13-19.9 Hz)	PDNC vs. PD-MCI -0.63 (-1.21, 0.04) PD-MCI vs. PD-D -0.70 (-1.57, 0.17) PDNC vs. PD-D -1.16 (-1.95, -0.37)
				GRP beta2 (20-30 Hz).	PDNC vs. PD-MCI -0.57 (-1.15, 0.02) PD-MCI vs. PD-D -0.81 (-1.69, 0.07) PDNC vs. PD-D -1.21 (-2.00, -0.41)
				Peak frequency at locations P3, P4 and Oz	PDNC vs. PD-MCI -0.90 (-1.51, -0.31) PD-MCI vs. PD-D -0.99 (-1.88, -0.10) PDNC vs. PD-D

					-1.88 (-2.54, -1.20)
Bonanni et al. 2008[2]	PD-DnF (19) PD-DF (16)	70.0[3]	PD-D (history of PD preceded dementia for at least 24 months); Cognitive fluctuations (CAF, *Walker et al. 2000*)	GRP theta (4.0-5.5 Hz)	PD-DnF vs. PD-DF 2.82 (1.88, 3.75)
				GRP pre-alpha (5.6-7.9 Hz)	PD-DnF vs. PD-DF 5.26 (3.86, 6.67)
				GRP alpha (8.0-12.0 Hz)	PD-DnF vs. PD-DF -8.40 (-10.47, -6.32)
				Mean frequency	PD-DnF vs. PD-DF -0.93 (-1.64, -0.24)
				DF in parieto-occipital derivations	PD-DnF vs. PD-DF -1.18 (-1.90, -0.46)
				DFV in parieto-occipital derivations	PD-DnF vs. PD-DF 1.19 (0.47, 1.91)
Fonseca et al. 2013	PD-D (12) PDwD (31)	70.3 68.1	Dementia (*Dubois et al. 2007*)	Mean absolute power delta (0.8-3.9 Hz)	PDwD vs. PD-D 0.85 (0.16, 1.54)
				Mean absolute power theta (4.29-7.8 Hz)	PDwD vs. PD-D 1.23 (0.52, 1.94)
Bousleiman et al. 2014	PD-MCI (41) PDNC (12)	67.2[3]	MCI (*Litvan et al. 2012*).	GRP alpha1 (8-10 Hz)	PDNC vs. PD-MCI -0.82 (-0.131, -0.001)
Gu et al. 2016[2]	PD-D (9) PD-MCI (17)	56.7[4] 62.1[4]	Dementia (DSM-IV); MCI (*Petersen et al. 1999*)	Beta (13-30 Hz) peak frequency[1]	PD-MCI vs. PD-D 1.10 (0.27, 1.92)
				GRP alpha (8-13 Hz)[1]	PD-MCI vs. PD-D -1.10 (-1.92, -0.27)
				alpha/theta ratio[1] - alpha (8-13 Hz) divided by theta (4-7 Hz)	PD-MCI vs. PD-D -1.10 (-1.92, -0.27)

Patients with PD-D were compared to PD patients without dementia in two studies (*Bosboom et al., 2006; Fonseca et al., 2013*). The latter group might include both PDNC and PD-MCI. However, global delta and theta powers (increased in PD-D patients) had the largest effect sizes. In one study, two sub-groups of PD-D patients were compared: patients with PD-D and cognitive fluctuations and patients with PD-D without cognitive fluctuations (*Bonnani et al., 2008*). Cognitive fluctuations are described as disorders of consciousness ranging from reduced arousal to stupor (*McKeith et al., 1996*). Global alpha and the so-called "pre-alpha" (5.6-7.9 Hz) powers had the largest effect sizes: alpha was decreased and "pre-alpha" increased in demented patients with cognitive fluctuations.

Topographic distribution of power spectra

Topographic distribution of spectral powers was addressed in 7 studies (*Morita et al., 2011; Bosboom et al., 2006; Bonanni et al., 2008; Bousleiman et al., 2014; Fonseca et al., 2009; Kamei et al., 2010; Ponsen et al., 2013*). Theta and alpha powers in temporal and parietal regions bilaterally had the largest effect sizes to distinguish between PDNC and PD-D patients. Theta power was increased and alpha power decreased in PD-D patients. Spectral ratio (sum of alpha and beta powers divided by the sum of delta and theta powers) in frontal regions and delta and alpha powers in posterior derivations had the largest effect sizes to distinguish between PD-MCI and PD-D. Delta power was increased and alpha power and spectral ratio were decreased in PD-D patients. Theta and beta powers and spectral ratio in posterior derivations had the largest effect sizes to distinguish between PDNC and PD-MCI. Theta power was increased and alpha power was decreased in PD-MCI patients. In one study PD patients with executive dysfunction were

compared to PD patients without executive dysfunction (*Kamei et al., 2010*). The largest effect size had spectral ratio in frontal derivations; spectral ratio was decreased in patients with executive dysfunction. Additionally, in one study PD-D patients were compared with PD without dementia (*Bosboom et al., 2006*). The largest effect sizes had alpha and delta powers in temporal, parietal and occipital regions, and beta and delta powers in central regions, and beta, alpha and delta powers in frontal regions. Delta power was increased, and alpha and beta powers were decreased in PD-D patients. Additionally, "pre-alpha" in frontal, temporal and parieto-occipital derivations had the largest effect size for distinguishing PD-D patients without cognitive fluctuations from PD-D patients with cognitive fluctuations (*Bonanni et al., 2008*). "Pre-alpha" power was increased in patients with cognitive fluctuations.

Correlation of power spectra with cognitive assessment tools

Correlation of spectral powers with different cognitive assessment tools and tests was analyzed in seven studies (Table 8). The mostly used tool for cognitive assessment in these studies was Mini-Mental State examination (MMSE). Positive Fisher's Z was observed for MMSE and spectral ratios at all scalp locations, and relative power in the range 8-13 Hz (alpha), and peak background frequency; while negative Fisher's Z was observed for MMSE and relative power in the range 0-4 Hz (delta). Negative Fisher's Z was observed for Cambridge Cognitive Examination (CAMCOG) and relative power in the range 4-8 Hz (theta) in bilateral occipital and right temporal regions. Additionally, in one study, correlation of median frequency with cognitive domains was investigated (*Zimmermann et al., 2015*). Significant correlations were observed for "episodic and long term memory domain", followed by "overall cognitive score", "fluency domain", "attention domain" and "executive functions domain". In one study no correlation of absolute power spectra with neuropsychatric inventory was reported in non-demented PD patients (*Fonseca et al., 2015*).

Table 8. Markers which significantly correlate with various cognitive assessment tools in PD.

**Original data not available in the publications. Fisher's Z calculated from correlation coefficient and sample size, according to Lipsey and Wilson 2001 (Practical Meta-Analysis (Applied Social Research Methods) 1st Edition).*

***Spectral ratio - sum of absolute power values for alpha (8.20-12.89 Hz) and beta (13.28-30.8 Hz) waves divided by the sum of absolute power values for delta (1.17-3.91 Hz) and theta (4.3-7.81 Hz)*

****Cognitive domain – combined parameter, including a set of cognitive tests, which indicates cognitive performance in certain categories.*

*****Combined score, including an average of 26 cognitive tests' results*

CAMCOG - Cambridge Cognition Examination; MMSE – Mini Mental State Examination.

Refs	Age, mean	N	Correlation	Fisher's z (95% CI)
Bosboom et al. 2006	71.7	13 PD-wD	Left occipital theta (4-8 Hz) vs. CAMCOG	-0.70 (-1.32, 0.08)
			Right occipital theta (4-8 Hz) vs. CAMCOG	-0.67 (-1.29, 0.05)
			Right temporal theta (4-8 Hz)	-0.68 (-1.30, 0.06)

Caviness et al. 2007	76.4	66 PD-wD	GRP delta (1.5-3.9 Hz) vs. MMSE	-0.51 (-0.76, -0.26)
			GRP alpha (8-12.9 Hz) vs. MMSE	0.34 (0.10, 0.59)
			Peak background frequency vs. MMSE	0.42 (0.18, 0.67)
Stoffers et al. 2008	59.4	18 *de novo* PD	Relative low alpha (8-10 Hz) vs. redundancy of the second order (Vienna perseveration) in bilateral central and parietal regions	-0.11 (-0.19, -0.01)
Morita et al. 2011	67.6	100 PD	Spectral ratio** at Fp location (electrode positions Fp1 and Fp2) vs. MMSE	0.30 (0.10, 0.50)
			Spectral ratio** at F location (electrode positions F3, F4, F7 and F8) vs. MMSE	0.32 (0.12, 0.52)
			Spectral ratio** at C location (electrode positions C3 and C4) vs. MMSE	0.28 (0.08, 0.48)
			Spectral ratio** at P location (electrode positions P3 and P4) vs. MMSE	0.32 (0.12, 0.52)
			Spectral ratio** at T location (electrode positions T3, T4, T5 and T6) vs. MMSE	0.32 (0.12, 0.52)
			Spectral ratio** at O location (electrode positions O1 and O2) vs. MMSE	0.35 (0.16, 0.55)
Babiloni et al. 2011	72.0	13 PD-D	Relative alpha1 (8-10.5 Hz) in parietal regions (Brodman areas 5, 7, 30, 39, 40, 43) vs. MMSE	0.35 (-0.27, 0.97)
			Relative alpha1 (8-10.5 Hz) in occipital regions (Brodman areas 5, 7, 30, 39, 40, 43) vs. MMSE	0.44 (-0.18, 1.05)
Fonseca et al. 2015	68.8	31 PD-wD	Absolute powers: delta (0.8-3.9 Hz), theta (4.29-7.8 Hz), alpha (8.2-12.5 Hz) and beta (12.9-36.3 Hz) vs. Neuropsychiatric inventory	No significant correlation with any marker
Zimmermann et al. 2015	67.6	48 PD-wD	Median frequency vs. Episodic Long term memory cognitive domain***	0.60 (0.31, 0.90)
			Median frequency vs. Overall Cognitive score****	0.51 (0.22, 0.80)
			Median frequency vs. Fluency cognitive domain***	0.41 (0.12, 0.70)
			Median frequency vs. Attention cognitive domain***	0.39 (0.10, 0.68)
			Median frequency vs. Executive cognitive domain***	0.35 (0.06, 0.65)

Additionally, longitudinal correlation of frequency results with cognitive states in PD using tools for cognitive assessment was assessed in 3 studies (*Bonanni et al., 2008; Olde Dubbelink et al., 2013a; Caviness et al., 2007*). In the first study (*Bonanni et al., 2008*), correlation with Frontal Assessment Battery scores was investigated: negative Fisher's Z was observed for power in the range 8-12 Hz (alpha), and positive Fisher's Z - for powers in the range 4-8 Hz (theta), over 2 years. In the second study (*Olde Dubbelink et al., 2013a*), various tools for cognitive assessment correlated with power spectra over 7 years of observation: negative Fisher's Z was observed: for global relative powers in the range 0.5-4 Hz (delta) and CAMCOG and Spatial Span Test; and for GRP in the range 4-8 Hz (theta) and CAMCOG, Pattern Recognition Memory, Semantic Fluency Test, and Spatial Span Test; and for GRP in the range 8-10 Hz (alpha1) and Spatial Working Memory. Positive Fisher's Z was observed: for powers in the range 8-13 Hz (alpha1 and alpha2) and 30-48 Hz (gamma) and CAMCOG, Pattern Recognition Memory and Spatial Span Test; and for powers in the range 4-8 Hz (theta) and Spatial Working Memory. In the third study (*Caviness et al., 2007*), correlation with power in the range 2.5-4 Hz (delta) was investigated: negative Fisher's Z was observed for MMSE, Rey Auditory Verbal Learning, Controlled Oral Word Association Test and Stroop test; while positive Fisher's Z was observed for Clinical Dementia Rating Sum of Boxes and Functional Assessment Staging Tool.

Hazard of conversion to dementia in Parkinson's disease

The relation of power spectra to conversion to PD-D was examined in 3 studies (Table 9). Hazard ratios of conversion to PD-D were analyzed in 2 studies. The hazard ratio of conversion to PD-D was significantly higher for patients with background EEG frequency below the median value of the entire sample at baseline (*Klassen et al. 2011*), and the theta power above the median value of the entire sample at baseline (*Olde Dubbelink et al. 2014a*). In one study, patients with PD-MCI, who converted to PD-D over two years had increased beta peak frequency, and decreased alpha relative power and alpha/theta ratio at baseline (*Gu et al. 2016*).

Table 9. Prediction of conversion to PD-D with spectral EEG markers

Author(s)	Duration of observation	Rates of conversion to PD-D over time	Hazard
Klassen et al. 2011	0.31 to 8.8 years with a mean of 3.3 years	The incidence of PD-D was calculated using the Kaplan-Meier method. The incidence of PD-D within 5 years of the baseline EEG examination was 34%.	Incidence of dementia within 5 years was: 66% for patients with background rhythm frequency below median of 8.5, 51% for patients with theta power above median of 19.
Gu et al. 2016	2 years	6 patients with PD-MCI converted to PD-D over a 2 year period	At baseline assessment beta peak frequency was significantly increased in the converted patients, and alpha relative power and alpha/theta ratio were significantly decreased.
Olde Dubbelink et al. 2014a	7 years	19 PD patients without dementia converted to PD-D over a 7 year period	At baseline assessment beta power was below median value of 27.96, peak frequency was below median value of 8.39, and theta power was above median of 22.85.

Brain functional connectivity and cognitive states in Parkinson's disease

Seven studies focused on functional connectivity features of cognitive states in PD (*Bosboom et al., 2009; Olde Dubbelink et al., 2014b, 2013b; Stoffers et al., 2008; Fonseca et al., 2013; Ponsen et al., 2013; Pugnetti et al., 2010*). Global field synchronization (GBS) was addressed in one study and coherence in another one. Patients with PD-D were compared with PD patients without dementia in both studies. PD-D patients had significantly higher GBS in theta frequency range ($p<0.02$) and lower GBS in the alpha1 range ($p<0.02$) (*Pugnetti et al., 2010*); higher frontal interhemispheric (F3-F4) and higher fronto-occipital intrahemispheric (F3-O1; F4-O2) coherence in in the beta frequency band was observed in another study (*Fonseca et al., 2013*).

In two studies SL was investigated. In one study correlation of connectivity markers with cognitive tests in PD patients without dementia and with varying disease duration was investigated (*Stoffers et al., 2008*). Higher level of perseveration executive task in patients with recently diagnosed PD (in the last 6 months before participation in the study) was associated with increased interhemispheric SL in alpha1 band. In an exploratory study by *Bosboom et al. (2009)* PD-D patients were compared to non-demented PD patients. Patients with PD-D had lower inter-hemispheric SL between temporal regions (frequency ranges: 0.5-4 Hz, 4-8 Hz and 8-10 Hz) and parietal regions (30-48 Hz); lower intra-hemispheric SL between frontal and temporal, and frontal and parietal regions in the left hemisphere (8-13 Hz), and frontal and temporal regions in the right hemisphere (8-13 Hz and 13-30 Hz). At the same time, higher intra-hemispheric SL was found between occipital and temporal, and occipital and parietal regions in the left hemisphere (13-30 Hz), and between parietal and occipital regions in the right hemisphere (8-10 Hz).

Phase Lag Index (PLI) was investigated in two studies. A comparison of PD-D patients with non-demented PD patients showed weaker PLI in fronto-temporal (0.5-4 Hz) and parieto-temporo-occipital (8-13 Hz) couplings in demented patients (*Ponsen et al., 2013*). In this study, general region-to-region connectivity was stronger in theta band and weaker in delta, alpha and beta bands in PD-D. A longitudinal observation of initially non-demented PD patients showed correlation of worsening of CAMCOG performance with a decrease of PLI in frontal and temporal regions in frequency range 8-10 Hz (*Olde Dubbelink et al., 2013b*). Finally, a graph theory analysis of longitudinal connectivity changes of non-demented PD patients was performed in one study (*Olde Dubbelink et al., 2014b*). Worsening of cognitive performance over time correlated with increase in eccentricity in the frequency range 8-10 Hz, and decrease of clustering coefficient and path length in the frequency range 4-8 Hz.

Chapter 5. Three-years follow up of patients with Parkinson's disease (clinical study)

The purpose of our study was to investigate clinical and qEEG (spectral) parameters as PD-D predictors, using high-resolution EEG with 256 electrodes and with fully automated removal of artefacts (*Hatz et al., 2015*). Our hypothesis was that qEEG variables at baseline are able to predict PD-D, and these qEEG variables are not influenced by clinical and demographic parameters. To address this research question a prospective (3 years) cohort of PD patients was assessed for potential neurological, psychological and neurophysiological risk factors.

Methods: enrollment of the patients

Patients were recruited from the outpatient clinic of the Department of Neurology and Neurophysiology of the Hospital of the University of Basel (Basel, Switzerland) in the period 2011 to 2012. Selection criteria: PD according to Queen Square Brain Bank criteria (*Hughes 1992*). Patients were excluded if they had dementia (DSM-IV), history of stroke, epilepsy, multiple sclerosis and surgical interventions to the brain, insufficient knowledge of German language. Patients underwent neurological, cognitive and neurophysiological (qEEG) examinations on inclusion (baseline) and after a mean time of 36 months (follow-up). Specialists who performed the assessment of the patients (neurologists, neuropsychologists and technicians) were unaware of the details of this study.

Standard protocol approvals, registrations, and patient consents

The research ethics committee of the cantons of Basel approved this study (Ethikkommission beider Basel, ref. No 135/11). All patients were fully informed of the nature of the study and provided written consent to participate.

Neurological assessment

Subsection III (motor examination) of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and Non-Motor Symptoms (NMS) scale were filled out. Levodopa daily equivalent dose of the antiparkinsonian medication (LED) was calculated (*Tomlinson et al., 2010*). Disease duration was assessed since the first symptoms of PD reported by the patient or caregiver.

Cognitive assessment

Cognitive evaluation was performed in individual sessions divided in three parts; each part with duration of approximately 90 minutes per day. The interval between the parts of each session was between 24 and 48 hours. MMSE and a battery of 14 cognitive tests were applied. Test variables were normalized with reference to a normative data base of 604 healthy controls from the Memory Clinic, Felix Platter Hospital of Basel, Switzerland (*Berres et al., 2000*). Cognitive tests were grouped in 6 cognitive domains (*Zimmermann et al., 2015*): attention, executive functions, fluency, long-term memory, working memory and visual-spatial functions (Table 10). A score reflecting cognitive performance in each domain comprised mean of the constituent test variables. An overall cognitive score (OCS) comprised a mean of all 14 cognitive tests. PD-associated mild cognitive impairment (PD-

MCI) was diagnosed under the MDS Task Force criteria (*Litvan et al., 2012*). Patients, who did not fit to the criteria of PD-MCI, were considered as cognitively normal (PDNC). Mood and behaviour was assessed with tests: Beck Depression Inventory version II (BDI-II), Obsessive-Compulsive Inventory (OCI), and compartment "Emotional well-being" of the Parkinson's disease Questionnaire with 39 items (PDQ39-EWB).

Table 10. Cognitive tests and cognitive domains.

Domain	Tests within a domain
(1) Attention	• Stroop Color-Word: time for color naming • Trail-Making: time for part A • Digit Span: correct backward
(2) Executive functions	• Trail-Making: time for part B divided by time for part A • Stroop Color-Word: time for interference task divided by time for color naming • Wisconsin Card Sorting: number of errors
(3) Fluency	• Phonemic verbal fluency: correct answers • Semantic verbal fluency: correct answers
(4) Long-term memory	• Verbal Learning – long-delayed recall • Verbal Learning – discrimination
(5) Working memory	• Corsi blocks: correct forward • Divided attention: omissions
(6) Visual-spatial functions	• Block design • Rey-Osterrieth complex figure copy

Neurophysiological assessment

Continuous EEG with 256 electrodes was recorded in relaxed eyes-closed state of the patients (Net Station 300; Electrical Geodesics, Inc). Electrode located at CZ was used as reference. The sampling rate was set at 1000 Hz, oscillations were filtered with 2500 order least-square filter with band-pass 0.5 – 70 Hz, and notch 50 Hz. Spectral analysis was performed with „TAPEEG" toolbox (*Hatz et al., 2015*) by Welch method (*Welch, 1967*). Detection and removal of artefacts (e.g. eye blinks) was fully automated, by an independent component analysis. Channels with bad activations were interpolated by spherical spline method. Global relative median power (GRMP) was calculated in frequency ranges: delta (1 – 4 Hz), theta (4 – 8 Hz), alpha1 (8 – 10 Hz), alpha2 (10 – 13 Hz), and beta (13 – 30 Hz). Median frequency (MF) in the range 4 – 14 Hz was calculated from occipital electrodes as the 50% quantile of the power spectrum (Fig.7).

Blood sampling and genotyping

From each patients we collected 10 ml of intravenous blood. Ethylenediamine tetraacetic acid was added to blood as in vitro anticoagulant. Blood samples were frozen at -70 oC and then were sent via express shipping from the Hospital of the University of Basel to the Hertie Institute for Clinical Brain Research in Tübingen.

DNA was extracted by salting-out and ethanol precipitation. 1.875 μg DNA of each sample was subsequently shipped on dry ice to the genotyping facility at the Helmholtz

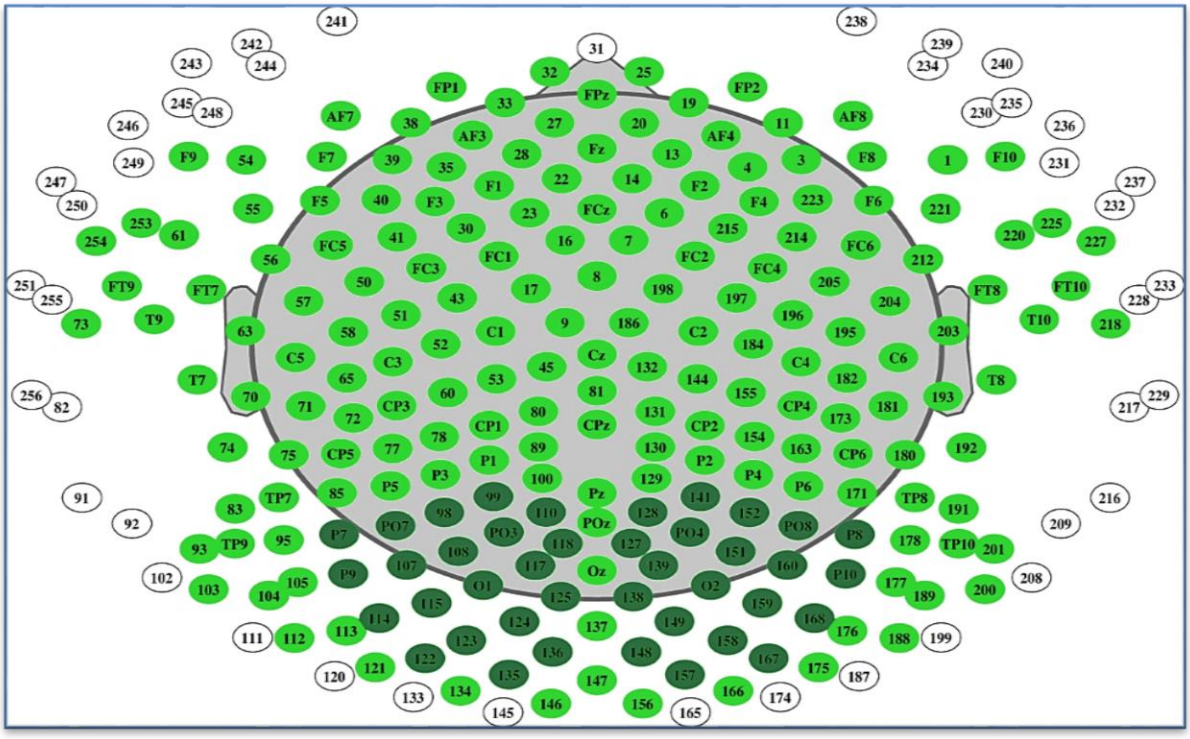
center Munich. The samples were then genotyped with the NeuroChip. This NeuroChip array was introduced in 2017 as a fast and efficient method for investigation of neurodegenerative diseases (*Blauwendraat et al., 2017*). TheNeuroChip backbone is based on a genome-wide genotyping array (Infinium HumanCore-24 v1.0) containing 306,670 tagging single nucleotide polymorphisms (SNPs) and a custom content that has been updated and extended with neurodegenerative disease-related custom content consisting of 179,467 SNPs. Of the variants, associated with neurodegenerative disorders, 348 SNPs were related with PD. Among the latter the following : LRRK2 (n=80), PINK1 (n=76), PARK2 (n=69), PARK7 (n=12), SNCA (n=5), other (n=106, including MAPT, GBA, APOE, COMT Intron rs2239393).

The genetic analysis of our sample of patients will be finished in Spring or Summer 2018. The results will be included in the cognitive risk score calculations and subsequently distributed as reports and publications.

Statistics

Statistical calculations were performed with R tool for statistical calculations v. 3.2.1. (*R Core Team, 2015*)The normality of the distribution of the data was tested with Shapiro-Wilk test. The influence of the baseline parameters on cognitive state at follow-up was checked with univariate and multivariate linear regression models with backward elimination. Prediction accuracy was checked with Receiver Operating Characteristic (ROC) curves. The results were additionally checked with Random Forest method with regression. The level of statistical significance was set at 0.05.

Figure 7. Electrode mapping of 256 electrodes.



Active electrodes colored in dark and light gray, occipital electrodes – dark gray.

Cognitive outcome

A change index in overall cognitive score (CI-OCS) was used as outcome. The CI-OCS was calculated as difference in overall cognitive score between follow-up and baseline, divided by the standard error of the difference (*Jacobson and Truax, 1991*).

Regression Models

The following baseline variables were considered as predictors: GRMP in ranges delta, theta, alpha1, alpha2, and beta, MF, cognitive domains: "attention," "executive functions," "fluency," "long-term memory," "working memory," and "visual-spatial functions," age, sex, highest educational level (measured in years), disease duration (years), duration of observation (years), LED, NMS,and UPDRS-III. Significant variables from the univariate regression models were included in multivariate models. To check the added value of the significant predictors to the cognitive task performance, non-normalized to 100% explained variance of the models was calculated. The relative importance of the variables was calculated with the R package "relaimpo" (*Grömping, 2006*) with method "LMG" and plotted in a bar diagram.

ROC-Curves

The ROC-curve analyses were performed with the R package "pROC" (*Robin et al., 2011*). We categorized the sample on the basis of MMSE score at follow-up (cut off <24).

Random Forest with regression

Random Forest (*Hastie et al., 2009*) is an ensemble machine learning method used for classifying data with high accuracy and for regression analysis. The goal of this method is to reduce the variance in the data and get a higher predictive performance of the model. This is done by using several decision trees, which are constructed based on subsets of the same training data, and then getting predictions on the test set based on the training. Each variable included in the model is evaluated based on its effect on the overall accuracy of the model and is ranked higher up if its exclusion results in a drop in the model accuracy. The role of each variable in the classification process is reflected in output measures called mean decrease accuracy (MDA) and mean decrease gini coefficient (MDGC). MDA is the increase in mean squared error of predictions after predictor variables being randomly shuffled. Higher the MDA, the more important is the variable. MDGC relates to the decrease of node impurity in the decision tree after each split, summed over all splits and trees. Higher the MDGC is, the more important the variable. Random Forest analysis was performed with the R package "randomForest" (*Liaw and Wiener, 2002*).

Results

Enrollment of the Patients

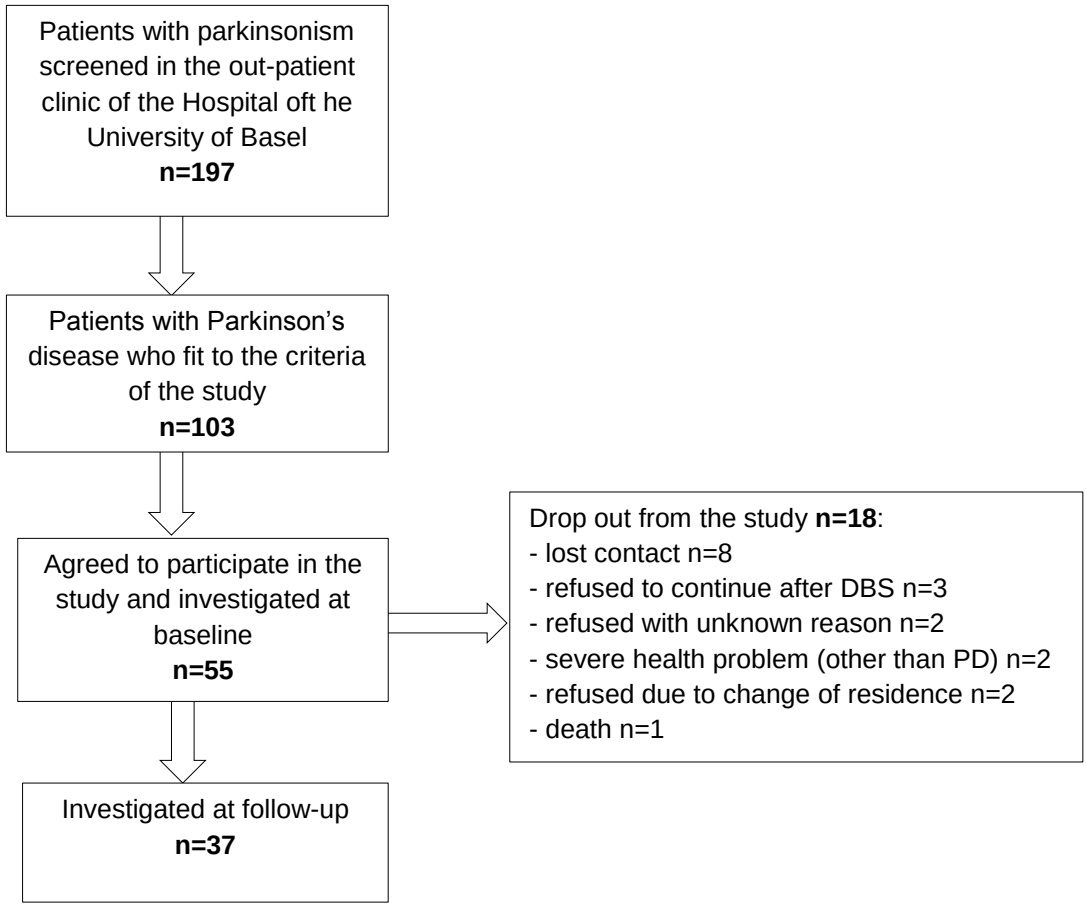
Between January 2012 and December 2013, 55 patients were selected in the study and assessed for neurological, psychological and qEEG parameters (Panel 3). At follow-up, cognitive outcome along with the other clinical data was obtained for 37 patients. Thus, these 37 patients were included in the analysis (Table 11).

Table 11. Sample at baseline.

For continuous variables presented as median and range (M [min, max]). GRMP, global relative median power; PDQ39, Parkinson's disease questionnaire with 39 items; UPDRS, unified Parkinson's disease rating scale.

Sex, males/females	25/12
Age, years	67 [31, 84]
Disease duration, years	8 [1, 20]
Duration of observation, months	37 [30, 44]
Education, years	14 [9, 20]
Beck Depression Inventory-II	6 [0, 15]
Obsessive Compulsive Inventory	6 [0, 25]
PDQ39 – emotional well-being	17 [0, 50]
UPDRS, Subscale III	14 [0, 50]
Levodopa equivalent, mg per day	691 [150, 2129]
Attention	-0.02 [-2.07, 1.13]
Executive functions	0.03 [-3.73, 1.17]
Fluency	-0.18 [-1.93, 1.61]
Long-term memory	-0.13 [-1.62, 2.60]
Working memory	-0.23 [-1.50, 2.37]
Visual-spatial functions	-0.23 [-2.60, 1.79]
Overall cognitive score	-0.10 [-2.05, 0.96]
Mini Mental State	29 [24, 30]
GRMP delta, %	22 [9, 42]
GRMP theta, %	18 [10, 46]
GRMP alpha1, %	18 [5, 33]
GRMP alpha2, %	13 [5, 33]
GRMP beta, %	20 [10, 38]
Median frequency, Hz	8.71 [7.14, 9.99]

Panel 3. Flow chart



Influence on CI-OCS

Regression analyses (Tables 12.1-4) identified three baseline parameters which had significant influence on CI-OCS: GRMP theta (β = -3.16, $p<0.001$), cognitive domain "executive functions" ($\beta = 0.54$, $p < 0.001$), cognitive domain "working memory" ($\beta = 0.19$, $p < 0.05$), adjusted R squared = 0.64, $p < 0.001$.

Table 12.1. Univariate regression models. In all models, CI-OCS was introduced as dependent variable.

Predictor	Estimate	Standard error	Adj. R-squared	F-statistic	t value	p-value
Age	-0.020	0.013	0.075	3.897	-1.974	0.0563
Sex (males)	-0.360	0.174	0.083	4.256	-2.063	0.0505
Education	-0.008	0.024	0.117	3.440	-0.307	0.0519
Duration of observation	0.037	0.286	-0.028	0.016	0.130	0.2575
Disease duration	-0.032	0.018	0.055	3.131	-1.770	0.0855
UPDRS-III at baseline	-0.017	0.009	0.067	3.590	-1.895	0.0664
LED at baseline	-0.000	0.000	-0.008	0.681	-0.826	0.4146

NMS at baseline	-0.002	0.004	-0.019	0.328	-0.573	0.5704
BDI-II at baseline	-0.020	0.020	-0.001	0.930	-0.965	0.3414
PDQ39EWB at baseline	0.000	0.006	-0.028	0.004	0.064	0.9495
MMSE at baseline	0.030	0.073	-0.023	0.169	0.411	0.6834
Attention at baseline	0.332	0.129	0.135	6.617	2.572	0.0145*
Executive functions at baseline	0.560	0.137	0.027	14.300	3.782	0.0005*
Fluency at baseline	0.381	0.134	0.164	8.070	2.841	0.0007*
Long-term memory at baseline	0.250	0.118	0.088	4.476	2.116	0.0415*
Working memory at baseline	0.3177	0.104	0.185	9.195	3.032	0.0045*
Visusal-spatial functions at baseline	0.3122	0.106	0.173	8.543	2.923	0.0060*
Delta at baseline	-0.379	1.413	-0.026	0.072	-0.268	0.7900
Theta at baseline	-3.289	0.900	0.255	13.360	-3.655	0.0008*
Alpha1 at baseline	1.434	1.296	0.006	1.225	1.107	0.2759
Alpha2 at baseline	3.247	1.650	0.073	3.871	1.968	0.0470*
Beta at baseline	3.364	1.553	0.093	4.692	2.166	0.0372*
Median frequency at baseline	0.387	0.148	0.138	6.791	2.606	0.0133*

Table 12.2. Multivariate regression model with significant cognitive predictors (domains: attention, executive functions, and fluency), selected in univariate models. CI-OCS was introduced as dependent variable.

Residual standard error: 0.5622, F-statistic: 6.332 on 3 and 33 DF, Adjusted R-squared: 0.3033, p-value: 0.001638.

Proportion of variance explained by model: 36.52%, metrics are not normalized.

Predictor	Estimate	Standard error	t value	p-value	Variance importance metrics, %
Attention at baseline	0.129	0.138	0.932	0.3583	7.36
Executive functions at baseline	0.427	0.159	2.684	0.0113*	20.01
Fluency at baseline	0.167	0.149	1.119	0.271	9.15

Table 12.3. Multivariate regression model with significant cognitive predictors (domains: long-term memory, working memory, and visual-spatial functions), selected in univariate models . CI-OCS was introduced as dependent variable.

Residual standard error: 0.5715, F-statistic: 5.768 on 3 and 33 DF, Adjusted R-squared: 0.2844, p-value: 0.002755

Proportion of variance explained by model: 34.38%, metrics are not normalized.

Predictor	Estimate	Standard error	t value	p-value	Variance importance metrics, %
Long-term memory at baseline	0.150	0.110	1.357	0.1840	6.96
Working memory at baseline	0.236	0.103	2.276	0.0295*	15.01
Visusal-spatial functions at baseline	0.193	0.108	1.778	0.0845	12.41

Table 12.4. Multivariate regression model with significant qEEG spectral predictors, selected in univariate models . CI-OCS was introduced as dependent variable.

Residual standard error: 0.5928, F-statistic: 3.688 on 4 and 32 DF, Adjusted R-squared: 0.2300, p-value: 0.01404

Proportion of variance explained by model: 31.52%, metrics are not normalized.

Predictor	Estimate	Standard error	t value	p-value	Variance importance metrics, %
Theta at baseline	-5.267	2.084	-2.527	0.0167*	17.67
Alpha2 at baseline	-4.4759	3.976	-1.126	0.2687	4.16
Beta at baseline	-2.034	2.398	-0.848	0.4026	4.05
Median frequency at baseline	0.195	0.435	0.449	0.6568	5.64

Explained variance of the overall model was 66.9%, of which "executive functions" made 27.5%, GRMP theta – 25.8%, and "working memory" – 13.6% (Table 13).

Table 13. Multivariate regression model with significant qEEG spectral and cognitive predictors. CI-OCS was introduced as dependent variable.

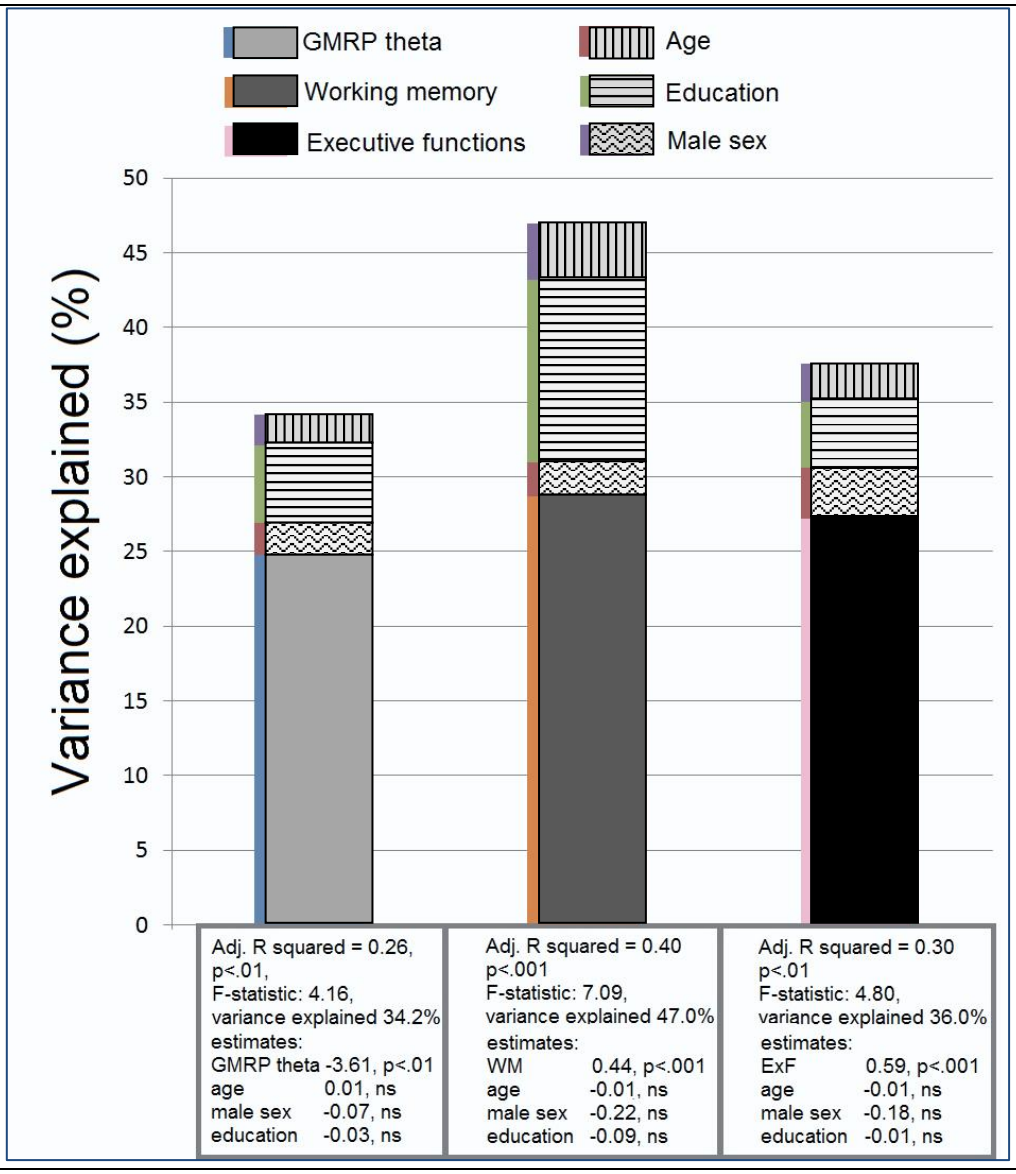
Residual standard error: 0.4057, F-statistic: 22.280 on 3 and 33 DF, Adjusted R-squared: 0.6394, p-value: 4.542e-08

Proportion of variance explained by model: 66.92%, metrics are not normalized.

Predictor	Estimate	Standard error	t value	p-value	Variance importance metrics, %
Theta at baseline	-3.157	0.641	-4.920	2.33e-05 *	25.79
Executive functions at baseline	0.544	0.106	5.127	1.27e-05 *	27.52
Working memory at baseline	0.187	0.072	2.588	0.0142 *	13.61

Additionally, we checked if age, sex, and education had confounding effect on each of the three significant variables (GRMP theta, "executive functions," and "working memory"). No confounding effects were identified (Figure 8).

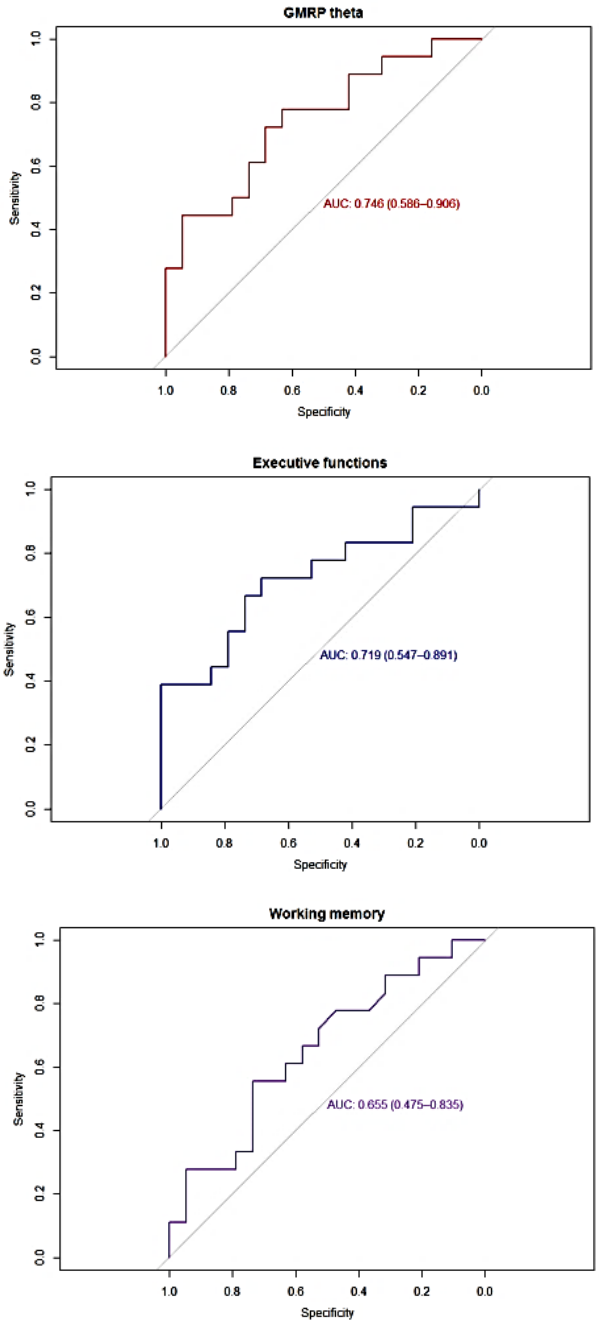
Figure 8. Results of the linear regression analyses.
Confounding effect of age, male sex, and education on the significant predictors of cognitive decline (GMRP theta, executive functions, and working memory). The variance of the models, that is explained by these predictors, is shown.



ROC-Curve Analyses

Receiver operating characteristic were built using variables: GRMP theta, "executive functions," and "working memory." Best accuracy was identified in GRMP theta: AUC = 75%, specificity = 63%, specificity = 77% (Figure 9).

Figure 9. Receiver operating characteristic (ROC)-curves analyses.



Coordinates	GMRP theta	Executive functions	Working memory
Area under the curve	0.746	0.719	0.655
Specificity	0.631	0.684	0.736
Sensitivity	0.777	0.722	0.555
Positive predictive value	0.666	0.684	0.666
Negative predictive value	0.750	0.722	0.636

Random Forest

Global relative median power theta was classified as the most important variable (MDA = 7.49, MDGC = 1.63) (Table 14).

Table 14. Random Forest analysis.

Type of random forest: regression
Number of trees: 1000
No. of variables tried at each split: 1
Mean of squared residuals: 0.2796442, % Var explained: 37.03

Predictors	Mean Decrease Accuracy	Mean Decrease Gini Coefficient
Theta at baseline	7.49	1.63
Alpha2 at baseline	4.28	1.20
Beta at baseline	4.98	1.29
Median frequency at baseline	1.79	1.27
Attention at baseline	2.91	1.40
Executive functions at baseline	7.29	1.67
Fluency at baseline	4.39	1.51
Working memory at baseline	3.69	1.51
Long-term memory at baseline	1.38	1.25
Visual-spatial functions at baseline	4.58	1.43

Chapter 6. Effects of deep brain stimulation in Parkinson's disease on psychiatric parameters with regard to age of the patients (clinical study)

Deep brain stimulation is widely used as neurosurgical treatment in PD, because it improves the motor manifestations of PD and reduces the need for antiparkinsonian medication (*Fasano and Lozano, 2015*). The intraoperative, short-term, and long-term adverse effects of DBS in PD are well known (*Falowski et al., 2015*). However, when candidates for DBS are appropriately selected, the benefit of the procedure in terms of an improved quality of life generally justifies its small risk. Moreover, it was concluded in the EARLYSTIM study (*Schuepbach et al., 2013*) that STN-DBS yielded a better outcome than drug treatment alone in patients with early (rather than advanced) motor complications of PD. In that study, the incidence of serious adverse events (SAE) was compared in patients in the medical versus the surgical arms of the study. The mean age of the 124 patients who underwent surgery was 52.9 years, and they were followed up for two years. Today, no consensus exists regarding an age cut-off for DBS as a treatment of PD (*Vesper et al., 2007; Floden et al., 2014*). In the present study, we retrospectively determined the incidences of SAE after STN-DBS in a group of patients whose mean age was 63.2 years and compared it to the incidence of SAE among the patients in the EARLYSTIM study.

Methods

Patients selection

We retrospectively analyzed the medical records of PD patients who underwent STN-DBS in our institution, which were extracted from the clinical and research databases of the University Hospital Basel. The study protocol was approved by the local ethics committee (Ethikkommission beider Basel). The records were analyzed for a period of two years after STN-DBS. The inclusion and exclusion criteria from the EARLYSTIM study (*Schuepbach et al., 2013*) were used to select cases for the analysis, with the exception of age: in the present study we focused on a group of relatively old operated patients (see Panel 4 for the criteria of selection). The age of the patients in the EARLYSTIM study ranged from 18 to 60 years, in the group of patients from our database, the age ranged from 58 to 70 years.

Panel 4. Selection criteria for the cases

The major inclusion criteria were adjusted to those, used in the EARLYSTIM study:

- diagnosis of idiopathic Parkinson's disease with a duration of at least four years before STN-DBS;
- STN-DBS was performed before 1 July 2013;
- moderate disease severity (i.e. Hoehn and Yahr score less than 3 in the "ON" medication state, assessed within 14 days before the STN-DBS).

The exclusion criteria were:

- dementia according to DSM-IV;
- a score of 25 or higher on the BDI-II;
- any psychotic disorder according to DSM-IV criteria.

Twenty six patients with PD (11 women, 15 men) who underwent STN-DBS in the period from January 1, 2008 to June 30, 2013, were selected for the analysis (i.e. the "BASEL group" of patients in what follows, as opposed to the "EARLYSTIM group").

Operative procedure for STN-DBS

In each patient, Medtronic 3389 electrodes were stereotactically implanted into the STN bilaterally under local anesthesia with the aid of intraoperative microelectrode recording and test stimulation, after coordinate- and visually-based target selection and trajectory calculation with the aid of preoperative computed tomography and magnetic resonance scans. The pulse generator was implanted subsequently under general anesthesia.

Analyses of the cases

Patients with PD who were scheduled for DBS underwent interdisciplinary assessment (including detailed neurological and neuropsychological examinations) before and, in general, every 6 months after the procedure. The results of these assessments were stored in the hospital's clinical and research databases and were compiled for this analysis. Whenever a patient needed his/her family doctor's assistance for problems potentially related to Parkinson's disease or to DBS, but was not admitted to the hospital for these problems, the family doctor reported such cases to the clinical and research database. The interdisciplinary assessment performed within the 14 days before the STN-DBS will be referred to as the "baseline assessment," while that performed 24 months later will be referred to as the "2-year assessment."

The following variables were analyzed: subscales II and III of the UPDRS, the Brief Psychiatric Rating Scale (BPRS), BDI II, and LED. In some cases, diagnoses made by other medical specialists (e.g., cardiologist) were used in addition as an indication of the patient's general medical condition.

SAE were defined according to the Medical Dictionary for Regulatory Activities, version 14.1, as any registered events that led to death, disability, or prolonged or new hospitalization with serious health impairment. The list of SAE was adjusted to the list of SAE described in the EARLYSTIM study. Thus, the SAE were grouped in the following categories: 1) suicide, 2) life-threatening events, 3) events related to medication or stimulation, 4) events related to surgery or device, 5) events related to PD. We calculated the number of reported SAE in each category for each patient within the 24 months after STN-DBS.

Statistical analysis

Statistical calculations were done with the R version 3.1.2 open source software. Baseline mean and standard deviations of the demographic and clinical parameters of the groups were compared with an unpaired Student's t-test. The numbers of patients with SAE were compared with the chi-squared test with Yates correction to prevent overestimation of statistical significance for small data; significance was set at $p < 0.05$. Linear regression models were applied to adjust for potential confounders in statistically significant differences.

Results

The results of comparison of the demographic and clinical features of the two groups are shown in Table 15. The patients in BASEL group were older than the patients in the EARLYSTIM study who underwent surgery (mean difference 10.3 years, 95% confidence interval (CI) 7.7 to 12.9). Disease duration in the BASEL group was longer (mean difference 2.7 years, CI: 1.3 to 4.1).

The results of the comparison of SAE incidence between the two groups are shown in Table 16. Significant differences in the incidence of SAE were found in the category "Event related to medication or stimulation" (Chi-squared=4.5, p=0.03) and in its subcategory "psychosis and hallucinations" (Chi-squared=24.7, p<0.01). The characteristics of psychosis and hallucination of the patients in the BASEL group are shown in Table 17. Regression models showed no influence of clinical and demographic parameters on the incidence of psychosis.

Table 15. Demographic and clinical features of the groups at baseline.
LEDD – levodopa equivalent daily dose; BPRS – Brief Psychiatric Rating Scale; BDI II – Beck Depression Inventory II; UPDRS –Unified Parkinson Disease Rating Scale.

Variable	EARLYSTIM STN-DBS	BASEL group	t-test
No of subjects	124	26	-
Males (%)	94 (75.8)	15 (57.7)	ns
Age (mean ±SD)	52.9 ±6.6	63.2 ±3.3	p<0.01
Duration of PD (mean ±SD)	7.3 ±3.1	10.0 ±3.7	p<0.01
LED (mean ±SD)	918.8 ±412.5	962.0 ±562.6	ns
BPRS score (mean ±SD)	25.3 ±1.0	24.8 ±5.1	ns
BDI-II score (mean ±SD) "ON" medication state	10.1 ±0.6	9.5 ±4.0	ns
UPDRS-II (mean ±SD)	15.0 ±0.8	15.4 ±5.8	ns
UPDRS-III (mean ±SD)	33.2 ±1.8	34.8 ±12.5	ns

Table 16. Serious adverse events.
*Worsening of mobility was defined as tremor, rigidity, akinesia, wearing off of medication effect, dystonia, or worsening of symptoms of PD.
**Dislocation of device was defined as dislocation of the stimulator, cable, or lead.
***Reoperation was necessary in order to repair the stimulator or lead.

Parameters	EARLYSTIM STN-DBS[2] (n = 124)		BASEL group (n=26)		Chi-square test, p value
Event	no. of events	no. of patients (%)	no. of events	no. of patients (%)	
Total serious adverse events	123	68 (54.8)	61	18 (69.2)	ns
1.Death, all by suicide	2	2 (1.6)	0	0	ns
2.Life-threatening event	14	12 (9.7)	2	2 (7.7)	ns
3.Event related to medication or stimulation	24	24 (19.4)	10	10 (38.5)	0.03
Worsening of mobility*	5	5 (4.0)	1	1 (3.8)	ns
Motor fluctuations	0	0	1	1 (3.8)	ns

Dyskinesia	1	1 (0.8)	0	0	ns
Psychosis or hallucinations	0	0	5	5 (19.2)	<0.01
Anxiety	0	0	0	0	-
Impulse control disorder	1	1 (0.8)	0	0	ns
Depression	6	6 (4.8)	2	2 (7.7)	ns
Suicidal ideation	1	1 (0.8)	0	0	ns
Suicidal attempt	2	2 (1.6)	0	0	ns
Cardiac disorder	0	0	0	0	-
Injury	3	3 (2.4)	0	0	ns
Respiratory or thoracic disorder	1	1 (0.8)	0	0	ns
Other	4	4 (3.2)	0	0	ns
4.Event related to surgery or device	26	22 (17.7)	8	8 (30.8)	ns
Impaired wound healing	4	4 (3.2)	2	2 (7.7)	ns
Intracerebral abscess or edema	2	2 (1.6)	2	2 (7.7)	ns
Dislocation of device**	5	4 (3.2)	1	1 (3.8)	ns
Reoperation necessary***	4	2 (1.6)	2	2 (7.7)	ns
Other	11	10 (8.1)	1	1 (3.8)	ns
5.Event related to PD	57	39 (31.5)	41	10 (38.5)	ns

Table 17. Patients with serious psychosis and hallucinations.

No	Age (years)	Sex	Clinical presentation	Time of manifest after STN-DBS	Result
1	60	female	Visual illusions, sense of presence, fear	8 weeks	New hospitalization
2	62	female	Delusion of spousal infidelity, suspicions of harmful thoughts	8 weeks	New hospitalization
3	60	male	Passage hallucinations, delusion	16 weeks	New hospitalization
4	69	male	Paranoia with aggression	10 days	Prolonged hospitalization
5	63	female	Visual illusions, sense of presence, fear	12 weeks	New hospitalization

Chapter 7. Effects of deep brain stimulation in Parkinson's disease on cognitive parameters with regard to age of the patients (clinical study)

Introduction

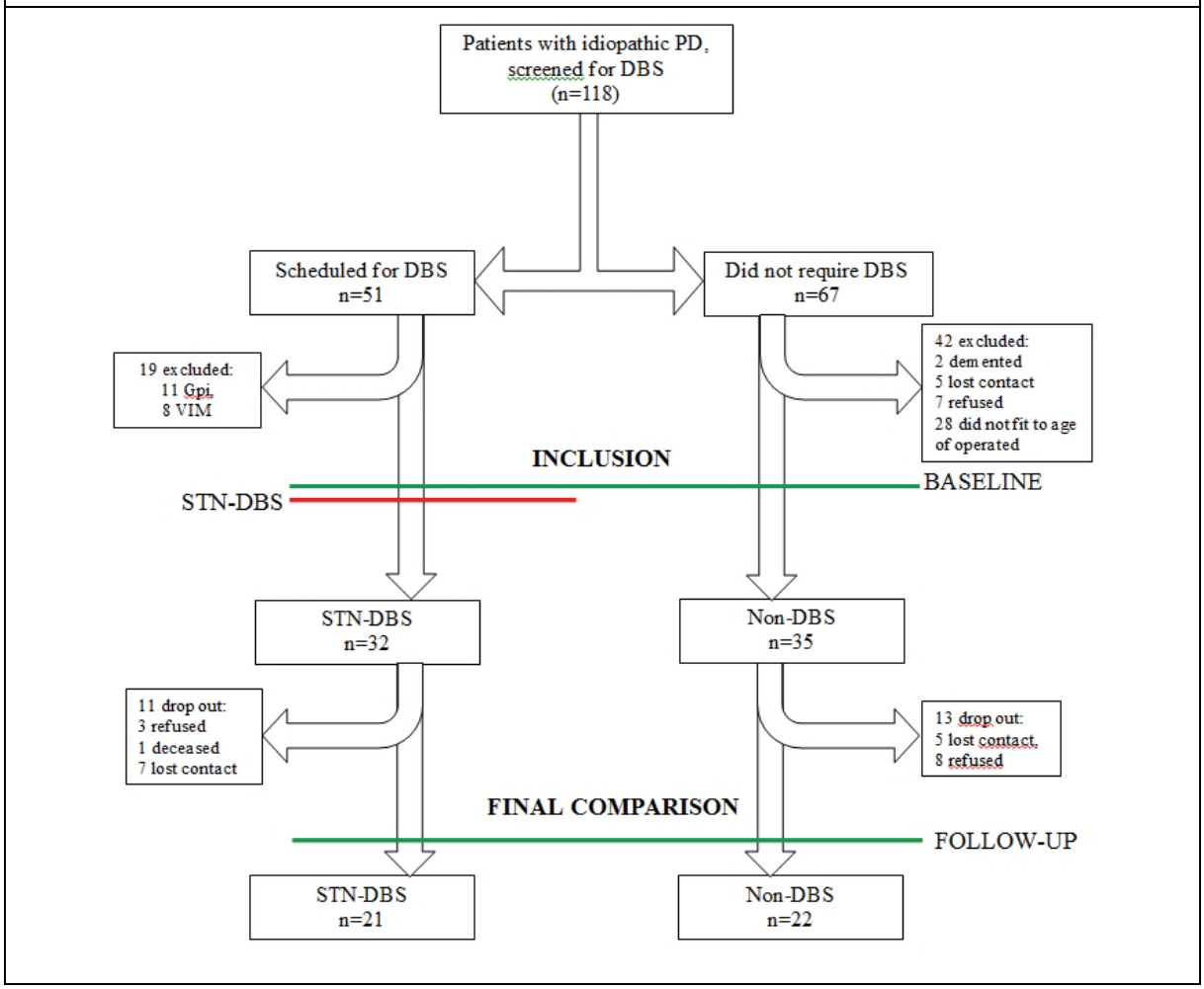
DBS alleviates motor symptoms of PD and allows patients to reduce their levodopa dose, thereby lessening side effects. DBS also improves patients' quality of life, especially if they have reached the plateau of oral medication (*Deuschl et a., 2006*). According to some reports, DBS is even superior to medical therapy in patients with PD and early motor complications (*Schuepbach et al., 2013*). DBS is not considered to cause major cognitive side effects, but some research groups have reported that it causes a decline in verbal fluency (VF) (*Saez-Zea et al., 2012*). The mechanism of the DBS-induced decline in VF is unclear (*Ehlen et al., 2014*). Some researchers suggest that it may be due to a "microlesion" of the brain tissue, produced by the passage of the electrodes during implantation (*Maltete et al., 2008*). Worsening fluency was associated with lower perfusion in the left dorsolateral prefrontal cortex, the anterior portion of the cingulate cortex, and the ventral portion of the caudate nucleus (*Cilia et al., 2007*). Other authors have suggested that the decline in VF may be directly due to the DBS procedure, but is rather related to the age of the patient (*Smith et al., 2014*). In this study, we investigated the possible impact of patients' age, level of education, disease duration, LED, disease progression (Hoehn & Yahr score, UPDRS- III), cognition (MMSE), and BDI-II on VF performance as outcome parameter, measured by a neuropsychological test battery after DBS in PD patients. We attempted to determine whether the decline in VF is caused by DBS itself or it, instead, reflects an influence of other factors.

Methods

Patients selection

Fourty three patients referred to the interdisciplinary team for functional stereotaxy at the Hospital of the University of Basel, Switzerland, were consecutively and prospectively included in the study from 2008 to 2014 (see Panel 5). The selection criteria were: clinically diagnosed idiopathic PD, no dementia or major ongoing psychiatric illness (according to DSM-IV), and adequate German language skills. The clinical diagnoses of idiopathic PD (*Hughes et al., 1992*) and assessments of disease severity were made by an experienced neurologist. The neurologist had no access to the patients' neuropsychological data. Twenty one patients who underwent STN-DBS were compared to 22 patients who did not undergo DBS. The study protocol was approved by the local ethics committee (Ethikkommission beider Basel, ref. No: 135/11). All patients provided their written informed consent. The characteristics of the two groups at baseline are shown in Table 18. Both groups underwent regular clinical follow-up and neurocognitive assessment.

Panel 5. Flow chart



Neuropsychological and neuropsychiatric assessment

All of the patients underwent cognitive evaluation by a neuropsychologist and a psychiatric evaluation by a psychiatrist. The MMSE was used as a screening tool for dementia.

Table 18. Characteristics of the patient groups at baseline.
*Medians and ranges are shown. * - chi-squared test for sex distribution in the two groups was used; ** - five missing; *** - four missing; ns = non-significant.*

Parameters	Non-DBS	DBS-STN	Mann-Whitney U-test
Number of patients	22	21	-
Age (years)	65.0 [46-77]	63.0 [49-74]	ns
Disease duration (years)	8.0 [4-22]	11.0 [4-18]	ns
Highest educational level (years)	14.0 [9-20]	14.0 [5-20]	ns
Sex (% male)	0.68	0.60	ns*
Levodopa equivalent dose (mg)	678 [100-4687]	960 [180-2342]	ns
Mini Mental State Examination	28.5 [27-30]	29 [27-30]	ns

Hoehn & Yahr scale	2 [1.5-3]	2 [1.5-3]	ns
UPDRS-III	16.5 [0-37]	18 [0-52]	ns
Beck depression inventory-II	7.0** [0-15]	6.8*** [1-18]	ns
Follow-up evaluation (months)	7 [4 – 10]	7 [4.5 – 10]	ns

The cognitive evaluation was performed with a battery of neuropsychological tests (*Lezak, 1995*), which were grouped in cognitive domains as suggested in *Zimmermann et al. (2015)*. Semantic and phonemic categories of VF were analyzed as outcome parameter. The cognitive performance of all subjects was analyzed at baseline – immediately before surgery in the STN-DBS group, and on enrollment in the study in the non DBS group – both at baseline and after a variable period ranging from 4 to 10 months. The median time of follow up in both groups was 7 months. To make the follow-up periods comparable, we used a reliable change index, as described by *Frerichs and Tuokko (2006)*.

Statistical analyses

Statistical calculations were done with the R version 3.1.2 free software. Sample parameters at baseline were evaluated after normalization, with two-tailed t-test. Chi-square tests were used to compare the sex distribution of the two groups. The cognitive test findings were subjected to the population-based standardization process described by *Berres et al. (2000)* with adjusted covariates including age, sex and educational level. Cognitive performance scores were compared with two-tailed t-test with confidence intervals and Bonferroni correction for multiple testing. The results are given as means and standard deviations and as medians and interquartile ranges. Linear regression model with stepwise backwards elimination was used to control for significant confounding effect on VF performance within and across the groups of patients; $p < 0.05$ was considered as statistically significant.

Results

Analysis of changes in cognitive performance over time by t-test. The patients' cognitive performance is shown in Table 19. After multiple corrections a significant decline was found only in the semantic category of VF in the STN-DBS group. The analyses using stepwise backward linear regression model was performed in pooled sample and across groups with VF performance as dependent variable. In the pooled sample significant effects of surgery, age, and combined age x surgery were detected. In the STN-DBS sample significant effects of age and disease duration were detected. In the non-operated sample none of the investigated parameters had significant confounding effect (Table 20).

Table 19. Cognitive tests at baseline and follow-up and cognitive change scores.
A positive change score means that cognitive performance improved, and a negative one means that it worsened. Negative mean differences in change score indicate poorer performance of the STN-DBS group.

Part 1.

Cognitive tests	Baseline			Follow-up	
	STN-DBS median [range]	**Non-DBS** median [range]	**p-value** t-test	**STN-DBS** median [range]	**Non-DBS** median [range]
Semantic category of verbal fluency	-0.40 [-3.5; 1.7]	-0.67 [-3.5; 0.9]	0.38	-1.24 [-2.9; 0.8]	-0.33 [-3.7; 2.3]
Phonemic category of verbal fluency	-0.10 [-4.1; 2.0]	-0.08 [-2.9; 2.0]	0.38	-0.67 [-5.0; 0.6]	-0.32 [-1.5; 2.5]
California verbal learning test	-0.50 [-3.0; 1.0]	-0.76 [-2.4; 0.7]	0.49	-0.10 [-2.8; 1.2]	0.33 [-3.0; 3.7]
Trail making A	0.00 [-2.1; 2.6]	-0.20 [-2.6; 1.9]	0.14	0.00 [-2.1; 2.2]	-0.15 [-3.4; 2.5]
Digit span backward	-0.36 [-1.7; 2.3]	-0.04 [-2.7; 2.3]	0.76	-0.36 [-2.3; 1.0]	0.04 [-1.7; 2.6]
Boston naming test	-0.30 [-4.8; 1.4]	-0.27 [-1.4; 1.0]	0.33	-0.24 [-2.9; 1.3]	-0.22 [-2.1; 1.2]
Rey-Osterrieth complex figure test	-0.30 [-2.1; 2.3]	-0.21 [-2.5; 1.4]	1.00	-0.25 [-3.3; 2.2]	0.10 [-2.8; 1.7]

Part 2.

Cognitive tests	Change Score				
	STN-DBS mean (standard deviation)	**Non-DBS** mean (standard deviation)	**Mean difference**	**p-value** corrected	**Cohen's d**
Semantic category of verbal fluency	-0.64 (1.14)	0.35 (0.90)	-0.99	<0.01	0.94
Phonemic category of verbal fluency	-0.52 (0.79)	0.09 (0.82)	-0.61	0.10	0.74
California verbal learning test	0.43 (1.28)	0.88 (1.12)	-0.45	0.41	0.46
Trail making A	-0.17 (0.81)	0.23 (0.75)	-0.40	0.81	0.51
Digit span backward	-0.20 (0.78)	0.18 (0.72)	-0.38	0.54	0.51
Boston naming test	-0.06 (1.15)	-0.01 (1.00)	-0.05	1.0	0.01
Rey-Osterrieth complex figure test	-0.06 (0.59)	-0.06 (0.96)	0	1.0	0.01

Table 20.

The results of the regression analyses predicting semantic fluency performance by potentially confounding factors are presented. Each row represents a linear regression model analysis predicting the variable in the first column. Columns 2 - 10 show estimates of the predictors with confidence intervals in parenthesis. The last column shows the overall model parameters. NA- not significant.

Semantic verbal fluency score in:	DBS surgery	Age x DBS surgery	Age (years)	Male sex	Educational level (years)	Disease duration (years)	Hoehn and Yahr score	MMSE score	UPDRS III score	BDI-II score	Model
- pooled sample (n=43)	ns	-0.34 (-0.09 to 0.10) p=0.003	ns	ns	ns	ns	ns	ns	ns	ns	Adjusted R^2=0.34; p<0.001
- STN-DBS (n=21)	-	ns	-0.08 (-0.11 to -0.004) p=0.006	ns	ns	-0.19 (-0.02 to -0.22) p=0.003	ns	ns	ns	ns	Adjusted R^2=0.49; p=0.004
- Non DBS (n=22)	-	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

Chapter 8. Olfactory deficits and quantitative EEG in patients with Parkinson's disease (clinical study)

The decline of olfaction is a feature of an early stage of PD, which may be useful as a premotor biomarker in PD (*Haehner et al., 2007; Chaudhuri and Odin 2010; Haas et al., 2012; Berg et al., 2013*), it is correlated with decrease hippocampal activity (*Welge-Lüssen et al., 2009*) and predicts brain atrophy (*Wattendorf et al., 2009*). In a recently suggested classification of the non-motor subtypes of PD, «Park weight subtype» concludes phenotypes with olfactory impairment and risk of dyskinesia (*Sauerbier et al., 2016b*). In addition, the olfactory decline may be helpful in differential diagnosis of PD (*Doty 2012*). Hyposmia has a high diagnostic accuracy, in comparison to other neurodegenerations; in PD the olfactory disturbance is much more severe (*Katzenschlager and Lees 2004; Silveira-Moriyama et al., 2009; Krismer et al., 2017*). The olfactory decline in PD also positively correlates with specific cognitive domains, such as executive function and episodic verbal memory (*Bohnen et al., 2010; Damholdt et al., 2011; Parrao et al., 2012*). Moreover, olfaction testing with University of Pennsylvania Smell Identification Test predicted cognitive decline after three years (*Fullard et al., 2016*). Cognitive decline in PD is associated with slowing of EEG, and this slowing can be identified with quantitative analysis of the EEG (*Caviness et al., 2007; Babiloni et al., 2011; Klassen et al., 2011*).

Thus, we assumed, that olfactory function in PD could correlate with cognitive performance and EEG parameters; and the combination of smell identification testing, cognitive assessment and EEG may increase the precision of PD identification and become a marker of higher risk of cognitive decline in PD patients. In this study, we aimed to compare olfactory function between PD patients and healthy controls to analyse correlations between the olfaction capacity, clinical features and EEG.

Methods

Patients selection

We performed a cross-sectional retrospective analysis of two samples of participants: PD patients and healthy controls. These participants were selected from a study database from the Hospital of the University of Basel, Switzerland according to the availability of the results of smell identification testing. The respective study is an ongoing observational cohort investigation, focused on the EEG and genetic markers of cognitive outcomes in PD; the details of this study are provided elsewhere (*Cozac et al., 2016*). The PD sample comprised 54 patients (median age 68 years, males 69%), and the HC sample comprised 21 participants (median age 67 years, males 67%). In both samples, we analysed the following baseline tools: Mini-Mental State Examination (MMSE), 5 neuropsychological tests, EEG, and olfactory «Screening 12 Test» («Sniffin' Sticks», commercially available, Burghart Messtechnik GmbH, Wedel, Germany). Only the PD sample was assessed with UPDRS. LED was calculated for all PD patients (*Tomlinson et al., 2010*). All participants provided written informed consent to the processing of personal data within the study, which was approved by the local ethics committee (Ethikkommision beider Basel, letters No 135/11 and 294/13).

Assessment of the olfactory function

The olfactory function was assessed using the «Sniffin Sticks Screening 12 Test» which consists of 12 felt-tip pens filled with an odorant, e.g. orange, coffee, fish (*Kobal et al., 1996*). Removal of the cap releases the odour. The type of the odorant is coded and is not known to the examinee. The pen is held approximately two centimetres in front of the examinee's nostrils, and the examinee receives a verbal command to inhale the odour with both nostrils for two seconds. Then the examinee is given a card with 4 variants of odour (including the correct one), and – in a forced choice paradigm - is asked to select the correct odour. The number of correctly identified odorants is summed up to calculate the «Sniffing score» (SnSc) ranging from 0 to 12.

EEG processing

We recorded continuous EEG with 214 active electrodes in each participant, in a relaxed eyes-closed state. The electrode located at C_Z was used as a reference (Net Station 300; Electrical Geodesics, Inc). All recordings were processed with "TAPEEG" toolbox (*Hatz et al., 2015*). The sampling rate was set at 1000 Hz, oscillations were filtered with 2500 order least-square filter with band-pass 0.5 – 70 Hz, and notch 50 Hz. Detection and removal of artefacts (e.g. eye blinks) were fully automated, by an independent component analysis. Channels with bad activations were automatically detected and interpolated by spherical spline method. Global relative median power (GRMP) was calculated in frequency ranges: theta (4 – 8 Hz) and alpha (8 – 13 Hz). Alpha/theta ratio (ATR) was subsequently calculated. In other words, ATR is an indicator of EEG slowing, the smaller the ratio, the slower the EEG.

Cognitive tests

We used the following 5 tests: Wisconsin Card Sorting Test: correct categories (WCST), Trail Making Test time for part A (TMTA), Test of Attentional Performance – Working Memory (2-back task): omissions (TAPWMO), Semantic verbal fluency test: correct answers (SVFC), and Phonemic verbal fluency: correct answers (PVFC). Test variables were normalized with reference to a normative database of 604 healthy controls from the Memory Clinic, Felix Platter Hospital of Basel, Switzerland (*Berres et al., 2000*).

Statistics

Statistical calculations were performed with R tool for statistical calculations (*R Core Team 2015*). We used corrected Wilcoxon and chi-squared tests to compare variables between the samples. Spearman rank correlation test was applied to check the relation of SnSc with the following parameters: age, sex, disease duration (since the first diagnosis), years of education, MMSE, LED, ATR, UPDRS-III, WCST, TMTA, TAPWMO, SVFC, and PVFC. We applied receiver operating ROC-curves to analyse the classification value of the following variables: SnSc, ATR and a combined score (SnSc+ ATR). For ROC-curve analyses, PD and HC samples were merged, and the presence of PD was used as an outcome. Bonferroni correction for multiple testing was applied. The level of statistical significance was set at .05.

Results

The samples are shown in Table 21. In comparison to HC, in PD patients the following parameters were significantly decreased: SnSc, WCST, TMT-A, and SVFT; and ATR was significantly decreased.

Table 21. Comparison of the PD-sample with HC-sample.

Comparison of the PD-sample with HC-sample. For continuous parameters Wilcoxon test with Bonferroni correction was applied; number of males was compared with Chi-squared test; ns = p>.05

Parameter	PD, n=54	HC, n=21	p value (95% conf.int.)
males, n (%)	37 (69)	14 (67)	ns
age, years	68 [45, 85]	67 [57, 78]	ns
years of education	15 [9, 20]	15 [10, 20]	ns
MMSE	29 [24, 30]	30 [26, 30]	ns
disease duration, years	3.41 [1, 23]	-	-
UPDRS-III	18 [1, 47]	-	-
LED, mg/day	475 [0, 2950]	-	-
SnSc	5.5 [2, 12]	10 [7, 12]	p<.001 (-5.0, -2.0)
WCST	-0.54 [-2.13, 3.23]	0.05 [-1.33, 2.17]	p<.05 (-0.9, -0.1)
SVFC	-0.30 [-2.08, 1.94]	0.11 [-1.42, 2.89]	p<.05 (-1.2, -0.1)
PVFC	0.22 [-1.95, 2.56]	0.22 [-1.72, 1.96]	ns
TMTA	-0.44 [-3.09, 2.27]	0.57 [-1.11, 3.34]	p<.01 (-1.5, -0.3)
TAPWMO	0.25 [-2.33, 2.80]	-0.10 [-2.33, 2.32]	ns
ATR	1.32 [0.24, 5.39]	1.96 [0.79, 7.71]	p<.05 (-1.0, -0.01)

In PD sample, SnSc correlated with age, disease duration, UPDRS-III, and the following items of UPDRS-III: “Postural stability” (rho=-0.43, p<.01), “Leg agility, right” (rho=-0.43, p<.01), “Gait” (rho=-0.29, p<.05), and “Rigidity neck” (rho=-0.30, p<.05) (Tables 22 and 23). In HC sample, SnSc correlated with age only (rho=-0.62, p<.05). No correlation of SnSc with ATR was identified in both samples.

Table 22. Correlation of SnSc with samples’ characteristics.

* - p<.05; ** - p<.01; *** - p<.001

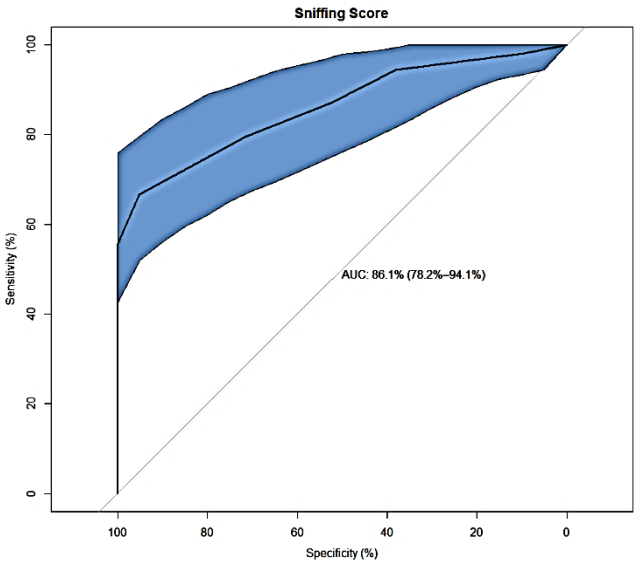
Parameter	Rho (PD sample)	Rho (HC sample)
male sex	-0.05	-0.29
age, years	-0.70***	-0.42**
years of education	0.23	0.21
MMSE	0.30	0.30
disease duration, years	-0.49***	-
UPDRS-III	-0.70**	-
LED, mg/day	-0.24	-
WCST	0.02	0.08
SVFC	-0.03	-0.08
PVFC	-0.20	-0.12
TMTA	0.25	-0.10
TAPWMO	0.25	0.10
ATR	0.23	0.20

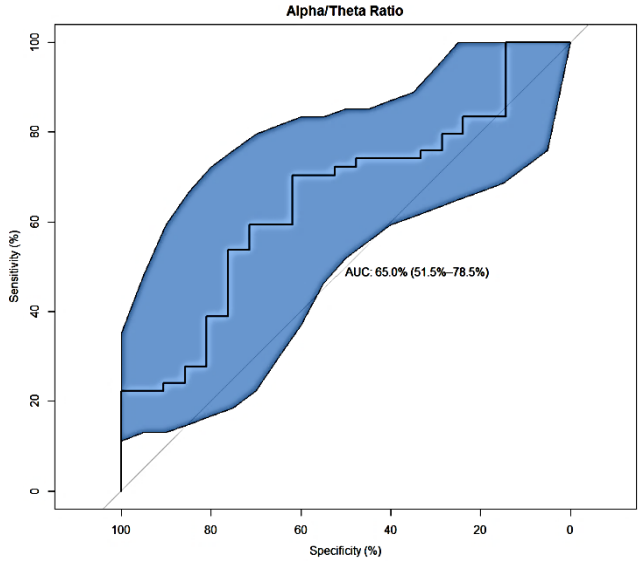
Table 23. Correlation of SnSc with items of UPDRS-III in PD sample.
* - p<.05; ** - p<.01; *** - p<.001

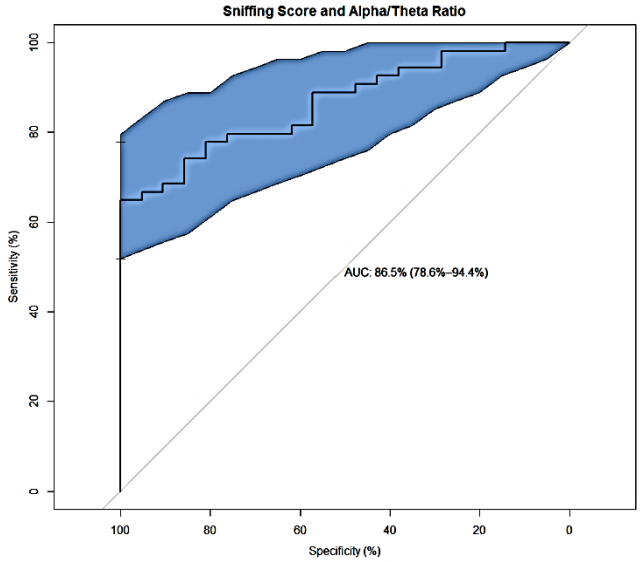
Items	**Rho**
speech	-0.15
facial expression	-0.23
tremor at rest: face	-0.14
tremor at rest: right upper extremity	-0.12
tremor at rest: left upper extremity	-0.05
tremor at rest: right lower extremity	-0.05
tremor at rest: left lower extremity	-0.01
action or postural tremor of hands: right	-0.08
action or postural tremor of hands: left	-0.22
rigidity: neck	-0.30*
rigidity: right upper extremity	-0.20
rigidity: left upper extremity	-0.19
rigidity: right lower extremity	-0.24
rigidity: left lower extremity	-0.24
finger taps: right	-0.05
finger taps: left	-0.10
hand movements: right	-0.12
hand movements: left	-0.12
rapid alternating movement of hands: right	-0.08
rapid alternating movement of hands: left	-0.24
leg agility: right	-0.43***
leg agility: left	-0.24
arising from chair	-0.12
posture	-0.25
gait	-0.29**
postural stability	-0.43***
body bradykinesia and hypokinesia	-0.23

The highest AUC was found in the combined marker (SnSc+ ATR): 86.5%, specificity 100%, sensitivity 64.8%); followed by SnSc (AUC 86.1%, spec. 95.2%, sens. 66.7%), and α/θ (65.0%, spec. 61.9%, sens. 70.3%), Fig. 10.

Figure 10. ROC-curves analyses.


Sniffing Score
Sensitivity (%)
Specificity (%)
AUC: 86.1% (78.2%–94.1%)
100
80
60
40
20
0


Alpha/Theta Ratio
Sensitivity (%)
Specificity (%)
AUC: 65.0% (51.5%–78.5%)
100
80
60
40
20
0


Sniffing Score and Alpha/Theta Ratio
Sensitivity (%)
Specificity (%)
AUC: 86.5% (78.6%–94.4%)
100
80
60
40
20
0

Chapter 9. Integrated discussions and conclusions

PD is a multifactorial neurodegenerative disorder featuring a range of motor and non-motor symptoms. PD comprises progressive cognitive and neuropsychiatric symptoms, which eventually result in PD-D. A number of factors may influence the risk of cognitive decline in PD, including genetic, neurophysiological, and psychosocial factors. The focus of this thesis was on contributing to the research on genetics and qEEG as the risk factors of PD-D. In addition, a number of clinical factors were also considered (DBS and olfaction), as these may be related with the risk of cognitive decline in PD.

Discussions

The discussions of the studies perfomed within this research are listed below.

In the study I, the results of our review support the idea that **spectral and connectivity markers have a significant impact in discriminating PD patients with different level of cognitive decline, regardless the variety of approaches to calculate these markers**. To summarize, a slowing of EEG frequencies correlates with a decline of cognition. Accordingly, an increase of spectral powers in the "slow" frequency bands < 8 Hz (delta and theta), and a decrease in the "fast" frequency bands > 8 Hz (alpha, beta and, less significantly, gamma), are spectral markers of PD-related cognitive decline. Topographically, occipital, parietal and temporal regions show the higher significance.

Additionally, the above mentioned spectral markers showed significant hazard ratio in predicting conversion of non-demented PD patients to PD-D. Patients with spectral powers in "fast" waves below, and in "slow" waves above the median values, have significantly higher risk of developing PD-D within two to seven years.

The connectivity patterns of the PD patients with cognitive impairment show changes in the same frequency ranges, where spectral markers of cognitive decline are identified: **mostly in theta (4-8 Hz), alpha1 (8-10 Hz) and beta (13-30 Hz) ranges**. The connectivity patterns of PD patients with cognitive decline changed in frontal, temporal, parietal and occipital regions. However, the number of connectivity studies focusing on cognitive states of PD patients is still very small; by the same token the studies had different setting and various connectivity markers were investigated. A common trend of cognitive decline in PD seems to be a decrease of connectivity in parieto-temporo-occipital regions.

The qEEG potentially has high test-retest reliability, reflects cortical function, requires little cooperation, is non-invasive, easily to repeat, and avoids learning bias and restricted availability associated with some neuropsychological testing. In sum, qEEG markers could be a valuable aid for diagnosing and predicting PD-related cognitive decline. Furthermore, it may allow for timely selection of patients prone for pharmacological and non-pharmacological interventions of prevention at a very early stage of PD and thereby potentially improve clinical results. Further studies with larger cohorts and longer periods of observation are expected.

In the study II, **increase of GRMP theta (4–8 Hz), and decrease of cognitive performance in domains "executive functions" and "working memory" significantly predicted worse CI-OCS after three years.**

The findings in GRMP theta are in line with the data from cohort studies with semi-automated processing of EEG (*Klassen et al., 2011; Olde Dubbelink et al., 2014a*). Additionally, in cross-sectional comparisons between Parkinson's disease patients with dementia and matched healthy controls, spectral power in the frequency range below 8 Hz was significantly increased in demented patients (*Babiloni et al., 2011; Fonseca et al., 2013*). From a pathophysiologic perspective, EEG slowing in severe cognitive decline may be explained by disruption of thalamocortical circuits, and pathological synchronization of the brain motor systems with slow frequencies related to the sensory motor integration (*Steriade et al., 1990; Rossini et al., 1991*). We can speculate that these pathological changes precede clinical manifestation of cognitive decline in PD. With regard to cognitive factors, we found that worse scores in domains "executive functions" and "working memory" are significant predictors of cognitive decline. *Zimmermann et al. (2015)* in a cross-sectional analysis showed significant correlation of occipital median frequency with overall cognitive score, domains "executive functions," "long-term memory," "attention," and "fluency" in dementia-free patients with PD. *Olde Dubbelink et al. (2014a)* found that fronto-executive (spatial span score) and posterior (pattern recognition memory) significantly predicted PD-D. Impairment of the executive functions is common in the early stage of PD (*Kehagia et al., 2010*). However, the cognitive profile of early stage PD is heterogeneous, and the significance of domain-specific cognitive deficits in identifying patients with a risk of dementia is still studied (*Robbins and Cools, 2014*).

In the study III, **we found a higher incidence of psychosis and hallucinations after STN-DBS in a sample of PD patients, who are about 10 years older, compared to the patients from the EARLYSTIM study**.

The effects of DBS on mental functioning are not clear, the pattern and expression of neuropsychiatric symptoms in operated patients with PD are highly variable (*Volkmann et al., 2010*). Some researchers have reported various types of psychiatric side-effects of DBS ranging from apathy and emotional lability to visual hallucinations, hypersexuality, and aggressive behavior (*Soulas et al., 2008; Le Jeune et al., 2009; Bickel et al., 2010; Daniele et al., 2012; Qureshi et al., 2015*). In a meta-analysis of 808 publications covering the time-period 1996 – 2005 the most common psychiatric side-effect associated with DBS was delirium, making 4 to 8% of all psychiatric complications (*Appleby et al., 2007*). Most of psychiatric post-DBS side-effects are transient and treatable (*Voon et al., 2006*), however, in some case reports these side-effects manifested in a very severe form with long-term consequences (*Zonana et al., 2011; Piccoli et al., 2015*). Other researchers reported an improvement of psychiatric symptoms after DBS (*Funkiewiez et al., 2004*). *Vesper et al. (2007)* analyzed the outcomes of DBS in PD as a function of age, observing two groups of patients one year after surgery: those younger versus those older than 65 years. Frequent transient neuropsychiatric impairment was seen in both groups (the adverse events were not stratified with regard to severity). In another observational study by *Shiina et al.,*

(2015) a sample of PD patients with mean age of 65 years was followed-up for 12 months after DBS. In that study, some of the patients experienced an improvement of pre-operative psychiatric symptoms, some had psychiatric side-effects, and others had no changes in psychiatric state. *Piasecki and Jefferson (2004)* proposed three possible mechanisms of mental disturbance after DBS: effects of the electrode placement itself, neurotransmitter changes induced by stimulation, and worsening of a pre-existing mental disorder by DBS. There were described 3 regions in the STN, in which the neurons make part of the following functional circuits: sensorimotor (dorsolateral), motor (ventromedial) and limbic (medial) (*Romanelli et al., 2004*). Limbic circuits participate in emotional and behavioral control. The spread of electrical currents from the electrodes in STN after DBS may cause disturbances in limbic circuit, thus leading to psychiatric symptoms. Another theory explaining psychiatric complications after DBS is based on the imbalance between neuromodulators: gamma-aminobutyric acid (GABA) and glutamate. DBS leads to an increased activity of nigral GABAergic neurons and decreased activity of glutamate flow from the STN (*Malhi and Sachdev, 2002; Piasecki and Jefferson, 2004*). It is known, that dysfunction of these transmitters has been involved in psychiatric disorders (*Drevets et al., 1997*). Other possible explanation of post-DBS psychosis is the reduction or withdrawal of dopaminergic medication after the surgery (*Voon et al., 2006*). Finally, some researchers have seen a relation between post-DBS psychosis and pre-existing mental disturbances and have therefore stressed the importance of a thorough psychiatric assessment as a prerequisite for DBS surgery (*Kalteis et al., 2006*). We can hypothesize that psychiatric SAE in our study have multifactorial origin and could be explained by the fact, that older patients are less resistant to the surgical stress and their neuroplasticity is decreased, leading to a poorer ability to re-set the functional limbic circuit, affected by PD and DBS (*Saint-Cyr et al., 2000*). It should be noted that the STN is not the only possible target for DBS in the treatment of PD. In particular, DBS in the internal segment of the GPi has been found to be comparable to STN-DBS in terms of efficacy and safety (*Honey et al., 2016*). However, GPi-DBS has its own benefits and limitations (*Groiss et al., 2009*). Some centers favor the pallidal target for certain groups of patients (*Okun et al., 2009*).

In the study IV, **we found a statistically significant decline in the semantic category of VF in DBS patients at a median follow-up time of seven months after DBS surgery**.

A linear regression model showed a significant influence of age on this decline, but not of educational level, sex, disease duration, LED, disease progression and depression. We confirmed the findings of other research groups that VF declines in PD patients who undergo STN-DBS compared to PD patients who do not (*Saez-Zea et al., 2012; Ehlen et al., 2014; Smith et al., 2014*). VF decline is reportedly the most common type of executive cognitive decline after DBS (*De Gaspari et al., 2006; Weaver et al., 2009; Folett et al., 2010; York et al., 2008*). *Marshall et al. (2012)* found lower VF at 6 months in a group of PD patients who underwent STN-DBS compared to a control group that did not. They hypothesized that VF deficits are caused by dysfunction in the striatum and in the interconnection in the striatum and the frontal lobe. *Witt et al. (2008)* found that DBS patients maintained cognitive functioning overall, but with a significant declines in VF

compared to patients given the "best medical treatment" without surgery; they concluded that concluded that impaired VF probably does not reflect disease progression alone but is, rather, an effect of DBS. *Cilia et al. (2007)* studied PD patients 12 months after DBS with SPECT employing the tracer 99mTc-ethyl cysteinate dimerbicisate to assess perfusion changes and their possible correlation with cognitive decline. Worsening fluency was associated with perfusion decrements in the left dorsolateral prefrontal cortex, the anterior portion of cingulate cortex, and the ventral caudate nucleus. A meta-analysis of 28 studies, performed by *Parsons et al. (2006)* confirmed the decline in VF after STN-DBS. Only a few studies have addressed the question of a possible confounding effect of age on VF decline after STN-DBS in PD patients. The mechanism by which verbal frequency declines is unclear; one may hypothesize that dysfunction in the anterior cingulate region or in cortical—basal ganglionic circuits involved in the word retrieval process is involved. The effect of DBS on memory, if any, is inadequately known and still under investigation (*Hershey et al., 2003*). In the COMPARE trial *Okun et al. (2009)* compared the VF performance between PD patients with DBS to the STN and with DBS to the internal globul pallidus. The subjects were tested at seven months after surgery in four different conditions: with stimulation to the contacts providing optimal motor condition, ventral and dorsal to that, and in OFF-stimulation condition. A significant deterioration of VF was found in the STN group, this deterioration was persistent with stimulation OFF state. The authors suggested that VF decline is induced by surgery rather stimulation. Later, *Mikos et al. (2011)* tested this hypothesis by generating patient-specific computer models of the STN DBS subjects from the COMPARE trial. These models included co-registration of the pre-operative magnetic resonance images, computed tomography scans, a 3D brain atlas, neurophysiological microelectrode recodrings, DBS electrode and the volume of tissue activated (VTA) at the STN. Worsening of VF correlated with larger VTA in ventral regions of the STN, but better VF correlated with VTA in dorsal regions. These findings might be related to the theory of functional subregions of the STN, which states that the sensorimotor functions are attributed to the layers localized dorsolaterally, and associative functions – to the layers localized more centrally and ventrally. Stimulation of the ventral subregion of the STN might, therefore, cause VF decline. Additionally, the hypothesis of the "lead implantation effect" to verbal fluency impairment was assessed by *Okun et al. (2012)* in an open-label randomized controlled trial. In their trial patients with PD underwent STN-DBS with subsequent randomization to a group with immediate constant-current stimulation activation and a group with delayed (three months) activation. The verbal fluency performance, measured by the Delis-Kaplin executive function scale, worsened similarly in both groups at 3 months follow up after implantation. After activation of the stimulation this impairment did not worsen further in the group with delayed activation. In addition, at one year follow up the verbal fluency decline in both groups did not recover and remained similar.

In the study V, **we found that odour identification capacity was significantly lower in PD patients than in HC, and decrease of olfaction correlated with motor impairment in PD, with gait and axial rigidity**.

The exact mechanism of the olfactory decline in PD is not fully clear; however, a detailed neuropathological staging concept was suggested by *Braak et al. (2003)*. Studies in European (*Verbaan et al., 2008*) and in Chinese populations (*Chen et al., 2015*) showed that olfactory impairment is related to advanced age in PD patients. In the American population of older PD-free persons the progression of parkinsonian signs positively correlated with an impairment of olfaction (*Wilson et al., 2008*). However, normal ageing is also associated with olfactory decline (*Murphy et al., 2002*). We may speculate that olfactory decline is faster in PD than in HC. It may be related to alpha-synuclein depositions in the olfactory bulb (*Ubeda-Banon et al., 2010*) and/or atrophy of the limbic cortex (*Wattendorf et al., 2009; Welge-Lüssen et al., 2009*). Association of olfactory impairment and mobility parameters may be explained by the projections from the olfactory tracts to the orbitofrontal cortex and cerebellum (*Doty 2003*). The latter regions of the brain are involved in the processes of mobility and gait (*Holtzer et al., 2014; Tian et al., 2017*). Interestingly, in a Japanese study olfactory function in PD patients with akinetic-rigid form of the disease was significantly lower than in patients with tremor-dominant and mixed forms (*Iijima et al., 2011*), and we also did not identify a significant correlation with tremor-related items of UPDRS-III. We may speculate that, in our study, the absence of association between olfaction and resting-state EEG may be partially explained by the fact, that the limbic system and olfactory bulbs are located deeper in the brain, thus electrical activity of their neurons cannot be properly registered as in the case of registration from the convexial cortex. Interestingly, in a cohort study, where the assessment of the olfactory function was combined with olfactory event-related potentials (OERP), a pattern of fluctuation of OERP was found over time (*Meusel et al., 2010*). The authors stressed that the elicitation of OERP is dependent on the integrity of the transducing (from the amygdala to higher cortices) structures of the brain. A neurodegenerative process, such as PD, may disturb these structures, thus influencing the functional connection between olfactory and EEG recordings.

Methodological considerations: strengths and limitations

As a general remark, it is also important to note, that the present research was designed within the constraints of a timeline of a doctoral study and available resources. With regard to the study I: First, there is no common opinion regarding which certain markers can be used to predict cognitive decline in PD. By virtue of various fast developing methods and approaches, different research groups investigate different methods: spectral markers, connectivity markers or their combination. In these conditions a thorough comparison of qEEG markers remains a challenge. However, future methods might further improve the validity of qEEG biomarkers of cognitive decline in PD.

Second, criteria for the diagnosis of PD-MCI are changing over time (*Ganguli et al., 2011; Petersen, 2004*). In some studies a simple cognitive screening is performed using Mini-Mental State Examination tool, in other cases a full cognitive assessment is performed with many cognitive tests. Since 2012 the Movement Disorders Society Task Force guidelines set a common criteria for PD-MCI (*Litvan et al., 2012*); however, the Diagnostic and Statistical Manual of Mental Disorders fifth edition has replaced the term MCI by "neurocognitive impairment" in 2013 (*Simpson, 2014*).

In sum, while differentiation between patients with PD with an intact cognitive state and patients with PD-D could be performed more or less clearly using qEEG markers, identification of the borderline level of cognition is relatively difficult.

With regard to the study II, while it is important for practical reasons to identify strong risk factors for dementia developing within one or two years, the short mean observation period of three years is a limitation of the study, and a longer follow-up is warranted. Another limitation is the relatively small sample size. The strength of the study II is the comprehensive neuropsychological and psychiatric assessments performed in this study. High GRMP theta, especially when combined with poorer cognitive scores in "executive functions" and "working memory," identifies patients with PD who are at a higher risk of progression to dementia.

Some methological considerations of the study II should be also mentioned. First, the patients from the BASEL group were not very old, but still within the generally accepted age limits for the operation (*Okun and Foote, 2010*). Second, while the EARLYSTIM data reflects a multicenter research, our analysis reports the findings in one single center. However, single-center analyses have a role in planning and powering of subsequent larger studies (*Bellomo et al., 2009*). This report may serve as a starting point for research into age-dependent effects of DBS in PD. Finally, a detailed comparison of cognitive performance of the patients in the two groups is impossible based on available information in the EARLYSTIM report. In spite of this limitation, comparing both groups allows to estimate the influence of age on neuropsychiatric and neuropsychological outcome of DBS surgery in patients with PD. The apparently higher incidence of psychiatric complications after STN-DBS in older patients underscores the need for comprehensive pre- and postoperative psychiatric assessment in older DBS patients. However, the psychiatric SAE that arose in our patients (the BASEL group) were transient, occurring mainly in the early postoperative period. The benefits of DBS clearly outweighed its adverse effects in this group of patients.

Some methodological considerations of the study IV should be noted. First, a 4- to 10-month period between surgery and follow-up evaluation is relatively short. Future research with long-term assessment would provide further information regarding the correlation of STN-DBS and cognitive functioning. Second, the patients from our STN-DBS group were not assessed in the 'OFF' stimulation condition; VF executive decline has been reported also in the 'OFF' stimulation state. Third, our small sample size limits the type of statistical analyses and the generalizability of our findings. Fourth, and perhaps most importantly, this was not a randomized study. DBS was performed or not performed according to clinical indications alone. The two groups of patients in the study were thus not comparable at baseline, in the important sense that all patients in the first group, but none in the second group, had been judged to be candidates for DBS on the basis of standardized clinical criteria. We therefore cannot be sure that the observed decline in VF was truly the result of DBS surgery or age itself. In spite of these limitations, our finding of a significant decline in the semantic category of VF in this relatively small sample highlights the sensitivity of this test for detecting cognitive changes after STN-DBS. We

found that the risk of VF decline after DBS surgery is greater the older the patients. At present, there is no precise age cut-off for DBS surgery. Studies in larger groups of patients for longer periods of observation are needed to determine whether the VF decline that is seen on relatively early follow-up might be a predictor of long-term cognitive performance in PD patients treated with STN-DBS. A screening tool with age-related cut-off values should be developed.

Finally, some methodological considerations of the study V should be mentioned. Firstly, the «Screening 12 Test» means «forced» selection of one correct odour of four on each of the 12 cards; thus there is a theoretical 25% chance of random selection of the correct answer. In this regard, a larger comprehensive olfactory test battery would allow a more precise identification of the level of hyposmia. Secondly, the UPDRS-III tool comprises a separate bilateral motor assessment, but the olfactory test which we applied assessed olfaction in both nostrils at the same time. An analysis of the association between sides of olfactory and motor impairment would be interesting. Lastly, a selection bias may be present because of the single-site cross-sectional setting of our study. Studies with larger samples and multiple centres could overcome this limitation.

A final important issue regarding all studies in this work concerns the possible effects of antiparkinsonian medication on cognitive symptoms within PD. It should be mentioned, that we statistically checked such effects with regression models (LEDD introduced as predictor in the models). We may speculate that antiparkinsonian medication has little, if such, effects on cognition in PD (as previously suggested by some colleagues, e.g. *Stam 2010; George et al., 2013*) or that all patients in this work were in optimal medicated state. In the present studies all patients reported to be stable on their medication, patients who received anticholinergic drugs were not present in the sample. In this work, this issue was also discussed (Chapter 3. Influence of dopamine-replacement therapy on qEEG parameters).

Conclusions

Study I

In sum, changes in spectral powers, delta and theta, have the highest significance to discriminate between PD-D and dementia-free patients with PD, while changes in spectral powers, theta and alpha, have the highest significance to separate MCI from normal cognition in PD. Findings regarding discrimination between MCI and dementia in PD are less consistent within reports, though delta and beta powers showed good discriminative capacity. With regard to connectivity measures, PLI has the highest significance to discriminate between PD-D and nondemented patients with PD.

Study II

Patients who manifest a decrease in cognitive tasks: executive functions and working memory, and increase of global median relative theta power, should be targeted for future early therapeutic intervention and disease modification. Perhaps, a combination of neurocognitive tests with qEEG improves identification of patients with PD and higher risk of cognitive decline.

Study III

The higher incidence of STN-DBS-related psychiatric complications underscores the need for comprehensive psychiatric pre-and post operative assessment in older DBS candidates. However, these psychiatric SAE were transient, and the benefits of DBS clearly outweighed its adverse effects.

Study IV

A significant decline in the semantic category of verbal fluency in this relatively highlights the sensitivity of verbal fluency testing for detecting cognitive changes after STN-DBS. Studies in larger groups of patients for longer periods of observation are needed to determine verbal fluency decline might be a predictor of long-term cognitive performance in PD patients treated with STN-DBS.

Study V

Because an olfactory decrease in PD correlates with motor impairment (especially axial signs), the assessment of olfactory function may be a useful additional tool in the detection and follow-up of PD, and may have a possible relation with the cognitive outcome at long-term follow-up.

General conclusion and future directions

The detection of cognitive impairment associated with PD is of upmost importance for future generations in terms of prevention of morbidity and mortality, social care and healthcare costs. Biomarkers that could identify PD patients with a risk of progression to PD-D early in the course of PD would potentially contribute towards the identification of novel treatment options. Future studies should involve the longitudinal assessment of participants (perhaps, longer than 5 years), to determine whether there is a relation between the increase of the EEG power of slow frequency waves, the severity of initial olfactory decline, gait impairment, and STN-DBS with cognitive decline, and whether the PD patients with abovementioned factors are associated with a more rapid cognitive decline and/or PD-D.

The heterogeneity of cognitive decline in PD means that is it unlikely a single biomarker will predict dementia risk, and hence, a composite biomarker is a realistic goal. It is important to stress, that each of the components of such composite biomarker should not bear similar information with regard to cognitive prediction, in other words: should not correlate between each other, but should reflect particular features of the cognitive course in PD. Importantly, changes of such markers should precede the clinical manifestation of cognitive decline in PD. Thus, these markers may become a valuable aid for timely selection of patients prone to pharmacological and nonpharmacological interventions of prevention at a very early stage of PD and thereby potentially improve clinical results. Prospective studies with larger cohorts investigating topographical scalp

distribution of qEEG changes as well as connectivity and its association with cognitive decline in PD are warranted.

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348) Williams-Gray CH, Mason SL, Evans JR, et al. *The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort.* **Journal of Neurology, Neurosurgery, and Psychiatry**. 2013; 84:1258–64.

349) Willis AW, Evanoff BA, Lian M, et al. *Metal emissions and urban incident Parkinson disease: a community health study of Medicare beneficiaries by using geographic information systems.* **American Journal of Epidemiology**. 2010;172:1357–63.

350) Wilson RS, Arnold SE, Buchman AS, et al. *Odor identification and progression of parkinsonian signs in older persons.* **Experimental Aging Research**. 2008;34:173–87.

351) Winblad B, Palmer K, Kivipelto M, et al. *Mild cognitive impairment—beyond controversies, towards a consensus: report of the international working group on mild cognitive impairment.* **Journal of Internal Medicine**. 2004; 256(3):240–6.

352) Winder-Rhodes SE, Evans JR, Ban M, et al. *Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort.* **Brain**. 2013;136:392–9.

353) Witt K, Daniels C, Reiff J, et al. *Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study.* **Lancet Neurology**. 2008;7:605–14.

354) Wong YC, Krainc D. *α-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies*. **Nat Med**. 2017;23(2):1–13.

355) Xie Y, Meng X, Xiao J, et al. *Cognitive Changes following Bilateral Deep Brain Stimulation of Subthalamic Nucleus in Parkinson's Disease: A Meta-Analysis.* **BioMed Research International**. 2016;2016:3596415.

356) York MK, Dulay M, Macias A, et al. *Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease.* **Journal of Neurology, Neurosurgery, and Psychiatry**. 2008;79:789–95.

357) Zarei M, Ibarretxe-Bilbao N, Compta Y, et al. *Cortical thinning is associated with disease stages and dementia in Parkinson's disease.* **Journal of Neurology, Neurosurgery, and Psychiatry**. 2013;84:875–81.

358) Zimmermann R, Gschwandtner U, Hatz F, et al. *Correlation of EEG slowing with cognitive domains in nondemented patients with Parkinson's disease.* **Dementia and Geriatric Cognitive Disorders**. 2015;39(3-4):207–14.

359) Zimprich A, Biskup S, Leitner P, et al. *Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology.* **Neuron**. 2004; 44(4):601–7.

360) Zlokovic BV. *Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders.* **Nature Reviews Neuroscience**. 2011;12:723–38.

361) Zonana J, Zimmerman M, McCarty SS, et al. *A case of abrupt-onset apathy, psychosis, and depression following deep brain stimulation in a patient with Parkinson's disease.* **Psychosomatics**. 2011;52:463–7.

362) Zou YM, Liu J, Tian ZY, et al. *Systematic review of the prevalence and incidence of Parkinson's disease in the People's Republic of China.* **Neuropsychiatric Disease and Treatment**. 2015;15:1467–72.

Supplements

Supplement 1. List of the excluded publications, Chapter 4

No	Reference	Cause of exclusion
1.	Kai T, Asai Y, Sakuma K, Koeda T, Nakashima K. Quantitative electroencephalogram analysis in dementia with Lewy bodies and Alzheimer's disease. J Neurol Sci. 2005;237(1-2):89-95.	Not focused on PD.
2.	Koenig T, Prichep L, Dierks T, Hubl D, Wahlund LO, John ER, Jelic V. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2005;26(2):165-171.	Not focused on PD.
3.	Babiloni C, Binetti G, Cassetta E, Dal Forno G, Del Percio C, Ferreri F, Ferri R, Frisoni G, Hirata K, Lanuzza B, Miniussi C, Moretti DV, Nobili F, Rodriguez G, Romani GL, Salinari S, Rossini PM. Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study. Clinical Neurophysiology. 2006;117(2):252-268.	Not focused on PD.
4.	Babiloni C, Frisoni G, Steriade M, Bresciani L, Binetti G, Del Percio C, Geroldi C, Miniussi C, Nobili F, Rodriguez G, Zappasodi F, Carfagna T, Rossini PM. Frontal white matter volume and delta EEG sources negatively correlate in awake subjects with mild cognitive impairment and Alzheimer's disease. Clinical Neurophysiology. 2006;117(5):1113-1129.	Not focused on PD.
5.	Prichep LS, John ER, Ferris SH, Rausch L, Fang Z, Cancro R, Torossian C, Reisberg B. Prediction of longitudinal cognitive decline in normal elderly with subjective	Not focused on PD.

	complaints using electrophysiological imaging. Neurobiol Aging. 2006;27(3):471-481.	
6.	Che H, Jung YJ, Im CH, Lee S. Extraction of qEEG variables to diagnose early dementia. Conf Proc IEEE Eng Med Biol Soc. 2007;2007:4115-4118.	Not focused on PD.
7.	Gawel M, Zalewska E, Szmidt-Sałkowska E, Kowalski J. Does EEG (visual and quantitative) reflect mental impairment in subcortical vascular dementia? J Neurol Sci. 2007;257(1-2):11-16.	Not focused on PD.
8.	Andersson M., Hansson O., Minthon L., Rosén I., Londos E. Electroencephalogram variability in dementia with Lewy bodies, Alzheimer's disease and controls. Dement. Geriatr. Cogn. Disord. 2008;26:284–290.	Not focused on PD.
9.	Luckhaus C, Grass-Kapanke B, Blaeser I, Ihl R, Supprian T, Winterer G, Zielasek J, Brinkmeyer J. Quantitative EEG in progressing vs stable mild cognitive impairment (MCI): results of a 1-year follow-up study. Int J Geriatr Psychiatry. 2008;23(11):1148-1155.	Not focused on PD.
10	Moazami-Goudarzi M, Sarnthein J, Michels L, Moukhtieva R, Jeanmonod D. Enhanced frontal low and high frequency power and synchronization in the resting EEG of parkinsonian patients. Neuroimage. 2008;41(3):985-997.	Not focused on cognitive states.
11	Onishi J, Suzuki Y, Yoshiko K, Hibino S, and Iguchi A. Predictive Model for Assessing Cognitive Impairment by Quantitative Electroencephalography. Cog Behav Neurol 2005;18(3):179-184.	Not focused on PD.
12	Roks G, Korf ES, van der Flier WM, Scheltens P, Stam CJ. The use of EEG in the diagnosis of dementia with Lewy bodies. Journal of Neurology, Neurosurgery, and Psychiatry. 2008;79(4):377-380.	Not focused on PD.
13	Rossini PM, Buscema M, Capriotti M, Grossi E, Rodriguez G, Del Percio C, Babiloni C. Is it possible to automatically distinguish resting EEG data of normal elderly vs. mild cognitive impairment subjects with high degree of accuracy? Clinical Neurophysiology. 2008;119(7):1534-1545	Not focused on PD.
14	Serizawa K, Kamei S, Morita A, Hara M, Mizutani T, Yoshihashi H, Yamaguchi M, Takeshita J, Hirayanagi K. Comparison of quantitative EEGs between Parkinson disease and age-adjusted normal controls. J Clinical Neurophysiology. 2008;25(6):361-366.	Not focused on cognitive states.
15	Gawel M, Zalewska E, Szmidt-Sałkowska E, Kowalski J. The value of quantitative EEG in differential diagnosis of Alzheimer's disease and subcortical vascular dementia. J Neurol Sci. 2009;283(1-2):127-133.	Not focused on PD.
16	Liedorp M, van der Flier WM, Hoogervorst EL, Scheltens P, Stam CJ. Associations between patterns of EEG abnormalities and diagnosis in a large memory clinic cohort. Dement Geriatr Cogn Disord. 2009;27(1):18-23.	Not focused on QEEG.
17	Morita A, Kamei S, Serizawa K, Mizutani T. The relationship between slowing EEGs and the progression of Parkinson's disease. J Clinical Neurophysiology. 2009;26(6):426-429.	Not focused on cognitive states.
18	Bonanni L, Franciotti R, Onofrj V, Anzellotti F, Mancino E, Monaco D, Gambi F, Manzoli L, Thomas A, Onofrj M. Revisiting P300 cognitive studies for dementia diagnosis: Early dementia with Lewy bodies (DLB) and Alzheimer disease (AD). Neurophysiol Clin. 2010;40(5-6):255-265.	Not focused on PD.
19	Schlede N, Zimmermann R, Ehrensperger MM, Gschwandtner U, Hardmeier M, Hatz F, Monsch AU, Naegelin Y, Fuhr P. Clinical EEG in cognitively impaired patients with Parkinson's Disease. J Neurol Sci. 2011;310(1-2):75-78	Not focused on QEEG.
20	Moretti DV, Zanetti O, Binetti G, and Frisoni GB. Quantitative EEG Markers in Mild Cognitive Impairment: Degenerative versus Vascular Brain Impairment. Int J Alzheimers Dis. 2012;2012:917537. doi: 10.1155/2012/917537.	Not focused on PD.
21	Snaedal J, Johannesson GH, Gudmundsson TE, Blin NP, Emilsdottir AL, Einarsson B, Johnsen K. Diagnostic accuracy of statistical pattern recognition of	Not focused on PD

	electroencephalogram registration in evaluation of cognitive impairment and dementia. Dement Geriatr Cogn Disord. 2012;34(1):51-60.	(patients with PD dementia and dementia with Lewy bodies were combined).
22	George JS, Strunk J, Mak-McCully R, Houser M, Poizner H, Aron AR. Dopaminergic therapy in Parkinson's disease decreases cortical beta band coherence in the resting state and increases cortical beta band power during executive control. Neuroimage Clin. 2013;3:261-270.	Not focused on cognitive states.
23	Han CX, Wang J, Yi GS, Che YQ. Investigation of EEG abnormalities in the early stage of Parkinson's disease. Cogn Neurodyn. 2013;7(4):351-359.	Not focused on cognitive states.
24	Lainscsek C, Hernandez ME, Weyhenmeyer J, Sejnowski TJ, Poizner H. Non-linear dynamical analysis of EEG time series distinguishes patients with Parkinson's disease from healthy individuals. Front Neurol. 2013;4:200.	Not focused on cognitive states.
25	Heinrichs-Graham E, Kurz MJ, Becker KM, Santamaria PM, Gendelman HE, Wilson TW. Hypersynchrony despite pathologically reduced beta oscillations in patients with Parkinson's disease: a pharmaco-magnetoencephalography study. J Neurophysiol. 2014;112(7):1739-1747.	Not focused on cognitive states.
26	Herz DM, Siebner HR, Hulme OJ, Florin E, Christensen MS, Timmermann L. Levodopa reinstates connectivity from prefrontal to premotor cortex during externally paced movement in Parkinson's disease. Neuroimage. 2014;90:15-23.	Not focused on cognitive states.
27	Melgari JM, Curcio G, Mastrolilli F, Salomone G, Trotta L, Tombini M, di Biase L, Scrascia F, Fini R, Fabrizio E, Rossini PM, Vernieri F. Alpha and beta EEG power reflects L-dopa acute administration in parkinsonian patients. Frontiers in Aging Neuroscience. 2014;6:302	Not focused on cognitive states.
28	Yuvaraj R, Murugappan M, Ibrahim NM, Sundaraj K, Omar MI, Mohamad K, Palaniappan R, Satiyan M. Inter-hemispheric EEG coherence analysis in Parkinson's disease: assessing brain activity during emotion processing. J Neural Transm. 2015;122(2):237-252.	Not focused on cognitive states.
29	Yuvaraj R, Murugappan M, Ibrahim NM, Omar MI, Sundaraj K, Mohamad K, Palaniappan R, Satiyan M. Emotion classification in Parkinson's disease by higher-order spectra and power spectrum features using EEG signals: a comparative study. J Integr Neurosci. 2014;13(1):89-120.	Not focused on cognitive states.
30	Yuvaraj R, Murugappan M, Omar MI, Ibrahim NM, Sundaraj K, Mohamad K, Satiyan M. Emotion processing in Parkinson's disease: an EEG spectral power study. Int J Neurosci. 2014;124(7):491-502.	Not focused on cognitive states.
31	Benz N, Hatz F, Bousleiman H, Ehrensperger MM, Gschwandtner U, Hardmeier M, Ruegg S, Schindler C, Zimmermann R, Monsch AU, Fuhr P. Slowing of EEG background activity in Parkinson's and Alzheimer's disease with early cognitive dysfunction. Frontiers in Aging Neuroscience. 2014 Nov 18;6:314.	Not focused on cognitive states.
32	Bonanni L, Perfetti B, Bifolchetti S, Taylor JP, Franciotti R, Parnetti L, Thomas A, Onofrj M. Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol Aging. 2015;36(1):434-445.	Not focused on PD.
33	van Dellen E, de Waal H, van der Flier WM, Lemstra AW, Slooter AJ, Smits LL, van Straaten EC, Stam CJ, Scheltens P. Loss of EEG Network Efficiency Is Related to Cognitive Impairment in Dementia With Lewy Bodies. Mov Disord. 2015 Jul 16. doi: 10.1002/mds.26309. [Epub ahead of print]	Not focused on PD.

34	Engedal K, Snaedal J, Hoegh P, Jelic V, Andersen BB, Naik M, Wahlund LO, Oeksengaard AR. Quantitative EEG applying the statistical recognition pattern method: a useful tool in dementia diagnostic workup. Dement Geriatr Cogn Disord 2015;40:1-12.	Not focused on PD.
35	Markser A, Maier F, Lewis CJ, Dembek TA, Pedrosa D, Eggers C, Timmermann L, Kalbe E, Fink GR, Burghaus L. Deep brain stimulation and cognitive decline in Parkinson's disease: The predictive value of electroencephalography. J Neurol. 2015 Jul 11. [Epub ahead of print]	DBS patients included.
36	Mostile G, Nicoletti A, Dibilio V, Luca A, Pappalardo I, Giuliano L, Cicero CE, Sciacca G, Raciti L, Contrafatto D, Bruno E, Sofia V, Zappia M. Electroencephalographic lateralization, clinical correlates and pharmacological response in untreated Parkinson's disease. Parkinsonism Relat Disord. 2015 Aug;21(8):948-953.	Not focused on cognitive states.
37	Song Y, Zang DW, Jin YY, Wang ZJ, Ni HY, Yin JZ, Ji DX. Background rhythm frequency and theta power of quantitative EEG analysis: predictive biomarkers for cognitive impairment post-cerebral infarcts. Clinical EEG and Neuroscience. 2015;46(2):142-146	Not focused on PD.
38	Swann NC, de Hemptinne C, Aron AR, Ostrem JL3, Knight RT, Starr PA. Elevated synchrony in Parkinson disease detected with electroencephalography. Annals of Neurology. 2015 Aug 20. doi: 10.1002/ana.24507. [Epub ahead of print]	Not focused on cognitive states.